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DIVISION OF RESEARCH SERVICES

ANNUAL REPORT

FY 1975



U.S. NIH

DIVISION OF RESEARCH SERVICES

Library  
National Institutes of Health  
Bethesda, Maryland 20014

Report of Program Activities  
July 1, 1974 through June 30, 1975

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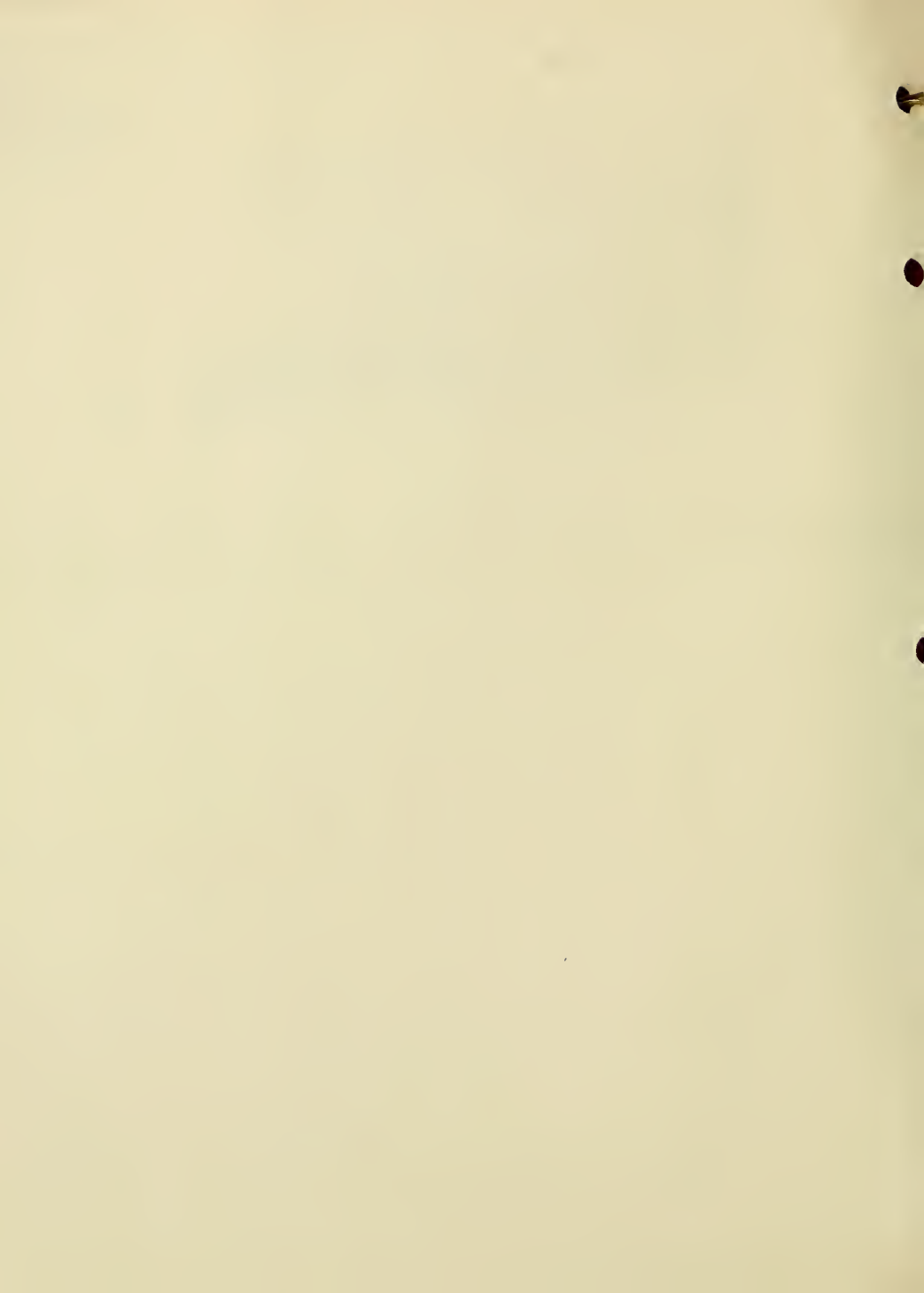
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# NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES -- DR. JOE R. HELD, DIRECTOR

Report of Program Activities  
July 1, 1974, through June 30, 1975.

## A. Objectives

The Division of Research Services supports other NIH components by providing centralized scientific, technical, and engineering services essential to biomedical research. Division programs function through a staff of professional and technical personnel organized into five functional areas: Biomedical Engineering and Instrumentation, Environmental Health and Safety, Library, Medical Arts and Photography, and Veterinary Resources.

## B. Current Programs

A broad range of central research support services and products are provided by the Division of Research Services. These currently include:

1. The application of engineering principles and techniques to the solution of biomedical problems.
2. The design, fabrication, and maintenance of special research instruments.
3. Environmental surveillance to detect and eliminate conditions adverse to conducting high quality research or hazardous to patients, employees, or the community.
4. Surveillance of biohazards, control of radioactive materials and maintenance of health and safety programs.
5. Library and bibliographic services.
6. Foreign language translation.
7. Still photography and motion picture production.
8. Graphics arts services and exhibits design.
9. Medical illustration and model making.
10. Animal production, procurement, conditioning and holding.
11. Animal health services.
12. Experimental surgery and related activities.
13. The production of tissue cultures, microbiologic medias and animal biologics.
14. Central processing and sterile preparation of laboratory glassware.

## C. Program Progress and Accomplishments

### 1. Biomedical Engineering and Instrumentation

Fiscal Year 1975 emphasized the refinement and extension of techniques innovated in previous years. Engineering design together with novel fabrication processes provided NIH with instrumental methods of unprecedented versatility. The ability of the Branch to promptly respond to intramural research demands was hampered by staff curtailments and associated personnel constraints; the quality of BEIB contributions, however, was not compromised.

Mathematically based systems modeling and prediction, verified for animals were successfully applied to human toxicology and therapy. Cytokinetic, pharmacokinetic, and pharmacodynamic bases for cancer chemotherapy were placed in quantitative perspective and used to explore alternative routes of drug administration, e.g., intrathecal and intraperitoneal, to seek optimal regimens. New methods for quantitative detection of trace metals in biological fluids were developed to better characterize environmental, diagnostic and therapeutic exposure of man to metallic ions.

Significant advances were achieved in ultrasonic imaging of structure and function in the cardiovascular system together with improved techniques for non-invasive blood flow measurement of unprecedented accuracy and precision. Ultrasonic methods were extended to ophthalmological scanning for diagnostic and therapeutic purposes. Quantitative measurements of cortical metabolism via televised fluoroscopy opened new avenues for the investigation of CNS physiology.

An important breakthrough was achieved by the completion of a microelectrode positioner that enables long term stable recordings of action potentials from a single neuron in the exposed pulsating cortex of animals and humans. A comprehensive set of instruments for ophthalmological surgery, including remotely controlled surgical tools, syringes, fluid exchangers and retinal suturing devices were provided to extend the capabilities of the eye surgeon and make his task easier.

## 2. Environmental Health and Safety Program

### a. Office of the Associate Director for Environmental Health and Safety

The transfer of the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, to the Division of Research Services as the Radiation Safety Program, took place on July 1, 1974. On the same date, the Safety Management Program transferred to DRS. On December 23, 1974, the Associate Director was appointed and given responsibility for the development of a well-integrated, comprehensive and centralized environmental health and safety program. Further progress toward centralization of functions was made on March 1, 1975, when the responsibilities for implementation of the National Environmental Policy Act (NEPA) were assigned to the Associate Director.

### b. Environmental Services Branch

Sixteen EPA effluent guidelines and several non-DHEW environmental impact statements were reviewed for the Office of the Assistant Secretary for Health, DHEW. Staff assistance was provided to the Division of Engineering Services in preparing the environmental assessment of the NIH Master Plan involving approximately sixteen construction projects.

Staff assistance was provided to the Assistant Director for Administration, NIH, in the Generic Analysis of all NIH programs. Staff also served on a task force of the Assistant Secretary for Health, DHEW, to develop proposed Departmental regulations and procedures for implementation of NEPA.



The national concern for employee health and safety was reflected in the ESB workload. Thirty-two employee requests were investigated concerning suspected hazards in their work places and three extensive surveys were conducted for requested Environmental Differential Pay. Three formal OSHA complaints were also reviewed and 108 other laboratory surveillance visits directly related to employee health were made.

#### c. Radiation Safety Program

The Nuclear Regulatory Commission issued seven licenses to NIH for the use of radionuclides. Possession of these licenses has greatly reduced the detailed problems of isotope procurement, but carries strict responsibilities governing use and ultimate disposal.

License renewals and amendments were obtained to permit the installation of two irradiators at the Clinical Center, one of 2400 curie capacity, the other of 500 curie.

Radioactive waste volume increased by 31% for the reporting period. Improvements in the waste handling area consisted of equipping the waste compactor with a HEPA filter to prevent radioactive aerosols from escaping into the work environment, and of installing a ventilated hood for the storage of volatile radioactive wastes.

Laboratory surveillance was maintained at a high level and carried out in the nearly 1500 areas where radioactive materials are being used. Strong emphasis was placed on the control of airborne radioactive substances. The number of air samples taken increased by 271% over the previous fiscal year. Investigation and remedial action took place where contamination was found.

The Radiation Safety Program continued to provide training in the safe handling of radioactive materials. Over 850 individuals attended training courses, most of them the one-day course entitled, "Radiation Safety in the Laboratory."

#### d. Safety Management Program

Accident investigations were conducted on a continuing basis by safety specialists. The NIH accident and injury reporting system continued during the reporting period to function on a recognized better level than most DHEW agencies. The close coordination of this activity with the Employee Health Service and other branches kept reporting close to 100%. Wherever necessary, remedial action was taken and recommendations were given. Fire prevention continued to be of major concern. A report, "NIH Fire Safety Posture", was completed. In it, each building on the NIH Bethesda location is described and discussed with regard to fire safety. The report provides a basis for eliminating fire hazards and for up-grading NIH facilities to prevent losses from fire.

There was a wide range of training activities throughout the year. An important part is the new employee orientation for Clinical Center and ADA personnel.

### 3. Library Branch

The Library Advisory Committee met three times during the year. Dr. Philip McMaster, NIAID, was appointed Chairman in February replacing Dr. John S. Finlayson, BB, who had served in that capacity for several years. At the same time the Committee was enlarged to 17 members with representation from all I/D's.

On February 24, the Supreme Court, by a tie vote four to four, with Justice Blackmun disqualifying himself, affirmed without opinion the U.S. Court of Claims decision in the case of Williams and Wilkins vs. the U.S. that large-scale unauthorized photocopying and free distribution of copyrighted medical journal articles by NLM and the NIH Library are not copyright infringements.

Effective November 1, the Technical Services Section was reorganized into two units, the Monographs Processing Unit and the Journals Processing Unit replacing the Acquisitions and the Cataloging Units.

The Library became a member of the Ohio College Library Center's shared cataloging automated network system through the Federal Library Experiment in Cooperative Cataloging.

A nonprint collection was organized. Current audiocassettes, tapes and slides were added to previous microform holdings and are available for use in the Library or for loan. Newly acquired nonprint items are included in the monthly memorandum of additions to the Library.

### 4. Medical Arts and Photography Branch

Demands for MAPB services increased approximately 25 percent in FY 1975. Physical consolidation of the graphics activities has satisfied the need for complete unity in graphics and statistical art preparation. With new equipment and wider use of contract service, delivering finished work has accelerated. Delivery of scientific photography has been reduced from 15 days to seven. Work has been done to establish graphic standards for statistical materials produced by the Branch. This is a forerunner of a continued drive to establish a unified visual communications system for the NIH.

### 5. Veterinary Resources Branch

VRB service functions continued to increase to meet demands of expanding intramural BID programs, although Branch personnel ceilings have been reduced 18 percent over the last seven years. Increased service with decreased personnel was accomplished by extensive use of overtime, improved animal production methods, automated processing of glassware and production of media, limited use of temporary positions, and contracting.

The VRB rodent breeding colonies were designated as a World Health Organization collaborating center in recognition of their importance as an international genetic repository. A committee of the National Research Council reviewed this effort and recommended that it be removed from the Service and Supply Fund and be given separate funding. More breeding nuclei

were provided this year to start new colonies outside NIH than have been requested in previous years. VRB colonies now serve as the genetic base for most NCI contract programs as well as the Frederick Cancer Research Center. The Catalogue of NIH Rodents was distributed internationally to over 1,000 researchers and specialists in fields of laboratory animal science. Twelve new rodent strains were added to the collection.

Open or complete disclosure formula rations for laboratory animal feeds developed by VRB permit competitive bidding for feed contracts, thereby reducing prices. Savings this year from conversion to open formula rations are estimated to be over \$100,000 compared to the estimated costs of closed formula rations purchased under noncompetitive contracts.

Pathogen-free rabbit and guinea pig colonies were successfully initiated this year. Nucleus colonies of guinea pigs were hysterectomy derived and established in the barrier in a clean, conventional area. An autoclavable diet for guinea pigs was successfully tested. Hysterectomy derivations were completed to establish all VRB rabbit strains in a new nonbarrier facility. They were foster nursed by SPF Edgewood Arsenal rabbits.

The Perrine Primate Center, established by DRS in FY 1974, is now stocked with 350 rhesus breeders and 75 squirrel monkeys. Two contracts were awarded in June 1974 for additional rhesus monkey breeding colonies. By FY 1978, these three DRS breeding operations are expected to supply 1,000 rhesus and 100 squirrel monkeys annually for intramural research.

Tissue culture and media production increased 7 percent. Blood agar plates were issued at a 7 percent increase also. Glassware issues increased slightly over last year, as did the use of disposable supplies. Surgical facilities were relocated from Building 28 to Building 14E, increasing capacity for surgical procedures.

#### D. Division Management

##### 1. Personnel Appointments

Mr. Levi C. Carter and Mrs. Rebecca Wilner were appointed during the year as the Division's Executive Officer and Personnel Officer, respectively.

##### 2. Equal Employment Opportunity

The Division's EEO Office and the Human Relations Committee (HRC) worked together to plan the second in a series of EEO Seminars around the theme "Think People." The success of the two sessions demonstrated the need to increase awareness of all DRS employees to the problems and frustrations experienced by employees and management alike.

The Division Human Relations Committee continued to keep the Director advised and aware of employee concerns. A compilation of these efforts was issued in an HRC report to all employees detailing the more significant actions initiated by the committee. The HRC also began holding its meetings in the various Branches and areas of DRS to afford a greater number of employees an opportunity to communicate their concerns to the committee.

In this regard also, suggestion boxes were installed in each Branch so that employees could relate concerns and problems to the committee and the EEO Office.

### 3. Employee Development

The Division's Training Office held interviews with all employees, GS-9 and below (and equivalents), to gather necessary data for formulating career development plans. This activity was coordinated with the Guidance and Counseling Branch, Division of Personnel Management.

Nineteen employees participated in the NIH Executive Development Program, coordinated by the Executive Management and Development Branch, DPM. These individuals, GS-12 and above (and their equivalents), completed individual development plans and remain active members in the program to develop managerial skills in executives.

Employee training activities were designed to meet individual as well as Division needs. Several female employees participated in programs designed for women in or aspiring to administrative/managerial/supervisory positions.

A well-balanced, incremental supervisors' training program was initiated within the Division. The DRS Supervisory Training Program, divided into modules, affords supervisors an opportunity to attend sessions to enhance their management skills and knowledge. More than 200 supervisors participated and have indicated approval of the program. Their evaluations led to constructive revisions and additions to the overall program.

### 4. Management Analysis Projects

The Management Analysis staff conducted a work improvement study of the Glassware Unit, VRB, to increase efficiency of the glassware processing system. Final recommendations centered on the redistribution of current manpower, installation of new automated systems, and modifications of current processing procedures. A work measurement study project quantified the time required to perform all end-product tasks during glassware processing. The data will establish more equitable rates for glassware sold under the Service and Supply Fund.

To increase effectiveness of the Small Animal and Glassware Billing Systems, the staff redesigned systems to include special reports for each group concerned with the sale of commodities from these activities. The new systems incorporate an improved distribution technique to automatically address each report system with the name and location of the individual receiving it. A variable message facility was also provided for the activity manager to communicate in written form with each customer of his service.

The Management Analysis staff provided consultative services to the Library Branch in acquiring an Automatic Circulation Control System. Through the efforts of the Management Analysis Office, the Division of Computer Research and Technology agreed to play a major role in acquisition, modification, and installation of a computerized Circulation Control System currently being run by the University of South Carolina.



## 5. Contracting and Materiel Management

More administrative time and attention were given to contracting operations because of the increased emphasis on securing outside services precipitated by the continued reduction in manpower over a period of years. For instance, operation of the NIH Perrine Primate Center was converted from an inhouse activity to contract because of staff shortages. Increased use of contracts for art and photography services has stimulated development of graphic standards for use by contractors. The Division Director's role as Chairman of the Primate Steering Committee broadened the Division's responsibility for such matters as establishment of a contract with the Pan American Health Organization for the development of New World monkey breeding stations in Latin America. Partial support for a international meeting on the primate resources also was provided to PAHO.

Contract support was given to the National Academy of Sciences for establishment of a committee on veterinary medicine. Increased emphasis was placed on the use of contracts for surveillance of laboratories, laboratory hoods and other equipment used in radiation, biohazard, and chemical carcinogenic activities. A new chemical waste disposal/recycling contract was awarded and attention was given to the possibility of contracting for total radioactive waste handling program.

The Division Administrative and Management Analysis Offices were contacts with the NIH Materiel Management System study group, primarily because of the existing BEIB computerized inventory system. The proposed computerized ordering receiving and inventory system appears to have high potential for benefiting NIH, if properly coordinated with all users of the system.

### E. Visual Communications Projects

The Visual Communications Project Officer provided consultation and advice on a wide variety of visual and editorial design projects. Included were scientific papers, slides and exhibits by investigators from DRS and other BID's, development of various training materials, and presentations on program and administrative matters.

Consultation was provided regarding the sound and visual presentation capabilities of alterations to Jack Masur Auditorium in the Clinical Center.

Continuing design and editorial assistance was provided the NCI in development of a series of slide/tape biohazard control and safety training packages. An additional presentation titled, "Hazard Control in the Animal Laboratory", was completed and released through the National Audio-Visual Center. Two additional scripts and story boards were assessed and edited; "Safety Standards for Research in Cancer" and "Assessment of Risk in the Cancer Virus Lab."

Editorial and format design assistance was provided for the "NIH Biohazards Safety Guide." It was released in loose leaf form for NIH laboratory use and in bound form for sale by the Superintendent of Documents, GPO.

A series of carcinogen warning symbols was developed for review and possible

use in research laboratories.

More material was added to a centralized file of original slides of DRS subjects. Slides were made available to a number of BID's for use in lectures and publications.

The Visual Communications Project Officer continued to lecture on effective communication techniques to NIH and NIH-related audiences. He served as Division contact for Freedom of Information Act affairs and also continued to coordinate and edit DRS scientific documents, reports, news stories, press releases, publications, and visual materials. Liaison was maintained with the NIH/OD, other BID's on reporting and informational matters, and representation was maintained with public interest groups such as the American Science Film Association and American Medical Writers Association. He also served on the science jury for CINE film awards and selection of U.S. motion pictures for use overseas.

A project which began 26 years ago at the time of the PHS Donora (Pa.) smog disaster study was completed as a visual comparison of conditions in pictures and sketches made from identical locations at Donora in 1949 and 1975. It was presented at the annual American Industrial Hygiene Conference.

## DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1974, through June 30, 1975

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH Dr. Lester Goodman, Chief

### I. SUMMARY

Fiscal Year 1975 emphasized the refinement and extension of techniques innovated in previous years. Engineering design together with novel fabrication processes provided NIH with instrumental methods of unprecedented versatility. The ability of the Branch to promptly respond to intramural research demands was hampered by staff curtailments and associated personnel constraints; the quality of BEIB contributions, however, was not compromised.

Mathematically based systems modeling and prediction, verified for animals, were successfully applied to human toxicology and therapy. Cytokinetic, pharmacokinetic, and pharmacodynamic bases for cancer chemotherapy were placed in quantitative perspective and used to explore alternative routes of drug administration, e.g., intrathecal and intraperitoneal, to seek optimal regimens. New methods for quantitative detection of trace metals in biological fluids were developed to better characterize environmental, diagnostic and therapeutic exposure of man to metallic ions. More reliable quantification of the interaction of polymeric materials with intracorporeal media enabled improved implant devices. Fluid mechanic analysis and physical models were effective in better explicating atherogenesis.

Significant advances were achieved in ultrasonic imaging of structure and function in the cardiovascular system together with improved techniques for non-invasive blood flow measurement of unprecedented accuracy and precision. Ultrasonic methods were extended to ophthalmological scanning for diagnostic and therapeutic purposes. Quantitative measurements of cortical metabolism via televised fluoroscopy opened new avenues for the investigation of CNS physiology. The patient electrical safety program was extended, better codified and advanced; versatile, new test apparatus was constructed and applied. NIH was provided with a variety of new systems for cell separation, biochemical analyses via NMR and calorimetry. Real-time physiological monitoring and display for surgery and patient care were improved significantly by innovative electronic and video methods.

Mechanization and automation of routine procedures provided for more economic utilization of manpower, dollars and materials especially in the area of processing samples for physical and chemical analysis. Devices were introduced to better protect personnel from the hazards associated with radioisotope administration. Substantial progress was attained and fresh directions of investigation established via new concepts and instrumentation for defining the electrical, chemical and physical concomitants of muscle contraction and nerve conduction in normal and traumatized tissues. An important breakthrough was achieved by the completion of a microelectrode positioner that enables long term stable recordings of action potentials

from a single neuron in the exposed pulsating cortex of animals and humans. A comprehensive set of instruments for ophthalmological surgery, including remotely controlled surgical tools, syringes, fluid exchangers and retinal suturing devices were provided to extend the capabilities of the eye surgeon and make his task easier.

The Scientific Equipment Rental Program continued to expand; it has been enthusiastically accepted and widely used by the NIH intramural research community as a reliable economic resource.



## II. BRANCH PROGRAMS

### A. Objectives

To provide direct and consultative engineering support to clinical and biomedical research projects, including advice on systems analysis, experimental design, and synthesis of technical expedients.

To design, develop, fabricate, and evaluate special-purpose devices and systems not commercially available.

To maintain and repair scientific laboratory and clinical equipment.

To obtain and disseminate information on developments and improved production methods in the biomedical engineering and instrumentation fields.

### B. Current Programs

The primary purpose of the Branch is to provide service and support to the intramural program of the NIH. BEIB activities, therefore, are identified with many of the individual programs that constitute the intramural research effort. The overall Branch program is best described as the coordinated effort of its operating elements.

#### 1. Instrument Fabrication

Production, modification, and design of biomedical equipment and instrumentation systems requiring special tools and skills in the electronic, electrical, glass, mechanical, optical, rubber, plastics, welding, and sheet metal categories.

#### 2. Systems Maintenance

Maintenance and repair of biomedical equipment and instrumentation systems and instruction of technicians and scientists in the proper use and operation of especially complex instruments and devices.

#### 3. Supply

Acquisition and disposition of materials, parts, and equipment required for branch operations and maintenance of controlled inventory stocks and records.

#### 4. Engineering and Applied Science -

Chemical, Electrical and Electronic, and Mechanical:

a. Direct and consultative professional services for fundamental and applied projects relevant to biomedical research and health care at the NIH.

b. Research, design, development, and evaluation related to new instrumentation and equipment.

c. Communication between NIH and the scientific community on engineering support to biomedical research and clinical practice.

## 5. Satellites

These technical support units, composed of selected engineers and technicians with appropriate shop facilities, are located in certain areas where it is beneficial to make typical BEIB support and service immediately available via a controlled degree of decentralization. They are responsive to demands of local programs and operate as integral parts of the resident team but are administratively responsible to the central Branch. Each satellite is especially tailored to meet specific needs of the host institute or division, supplying it with advantages of a proprietary technical group while maintaining the chief benefits of centralized resources.

## C. Program Progress and Accomplishments

### 1. Technical Services

#### a. Instrument Fabrication Section

Backlogs increased markedly over the year due to reductions in manpower. Although quality was maintained, delays in responding to typical requests for fabrication increased to more than two months; patient care related projects continued to receive first priority. Substantial overtime enabled the section to complete 3600 jobs valued at \$900,000 compared with 3800 jobs valued at \$850,000 in FY 1974.

#### b. Systems Maintenance Section

First priority attention to patient care related requests and emergency demands, coupled with virtually complete elimination of preventive maintenance due to a shortage of personnel, increased response time for typical demands to an excessive two weeks; two days is considered reasonable. Greater use of overtime and more direct production by supervisory technicians enabled the section to perform 10,200 jobs at a cost of \$1,100,000 compared with 9,500 and \$1,000,000 respectively in FY 1974.

The Scientific Equipment Rental Program continued to expand over the year as summarized below:

	<u>July 1, 1974</u>	<u>July 1, 1975</u>	<u>Percent Increase</u>
Number of pool items	423	550	23
Dollar value	\$478,000	\$700,000	42
Number of items on rental	194	240	24
Utilization rate	46%	46%	0
	<u>FY 1974</u>	<u>FY 1975</u>	<u>Percent Increase</u>
Gross revenue	\$65,000	\$102,000	57
New equipment investment	\$17,500	\$ 43,000	146

Full realization of the potential value of this program to the NIH continues to be impeded by constraints on personnel and space.

### c. Supply Unit

The effort was made, throughout the year, to achieve greater economy by consolidating inventories in terms of capital investment and number of items carried. A comparison with FY 1974 operations shows a change in number of transactions processed from 21,000 to 22,000 with the value of goods sold increasing from \$373,000 to \$440,000 in FY 1975.

## 2. Engineering and Applied Sciences

### a. Chemical Engineering

Substantial progress was achieved in applying chemical reaction engineering to problems of drug, metabolic and environmental contaminant distribution in the body. Principles established in animals were demonstrated applicable to humans for both toxic effects and optimal therapeutic protocols. A pharmacokinetic model, originally developed on the basis of extensive studies in mice, was used successfully to predict priming doses and infusion rates necessary to achieve arbitrary plasma concentrations of methotrexate in individual patients. The dynamics of plasma concentration following infusion was investigated to provide safer and more reliable "rescue" therapy following large methotrexate dosage. Cytokinetic, pharmacokinetic, and pharmacodynamic bases of resistance to anti-cancer drug therapy were explored, and several pharmacokinetic factors placed in quantitative perspective. Alternate routes of drug administration, e.g., intrathecal and intraperitoneal, were studied to exploit possible therapeutic advantage and avoid toxic consequences.

Environmental, diagnostic and therapeutic exposure of humans to metallic ions and complexes requires more sensitive and reliable methodology for analysis and characterization. Flameless atomic absorption spectrophotometry was applied to quantitative trace analysis of platinum in biological fluids and tissues. Other elements measured in biological or biomedical materials by this technique include calcium, magnesium, silicon, copper, and iron; gallium is under investigation. An instrument was developed for electronic control of the furnace temperature program to enhance sensitivity and enable analysis of materials with different combustion characteristics.

Both our understanding of biomaterials and ability to design prosthetic devices were advanced. A study to elucidate the kinetic and thermodynamic mechanisms associated with phthalate plasticizers from vinyl plastics revealed that desorption rate into a pseudoserum was independent of flow rate but strongly dependent upon lipid concentration in the serum. Studies which explored the effect of antineoplastic drugs on wound strength have significant potential bearing on the conduct of early chemotherapy following surgery. The application of segmented polyurethane to biomedicine, pioneered by one of our staff, was advanced by numerous applications at NIH and elsewhere to heart assist devices, cannulas, heart valves, and other devices. Of particular relevance are ventricular-aortic bypasses and composite heart valves developed at NIH which have been successful in animal studies.

Shear stress distributions in costs of canine aortas were studied by electrochemical instrumentation in steady and pulsatile flow. Regions of high shear were shown to exist at flow divider tips and other sites of developing velocity profiles especially in the presence of intricate three-dimensional geometry, flow branching, separation and reversal during pulsations. Regions of high shear and regions of disturbed flow correlate with anatomical localization of atherosclerotic plaque.

Extensive consultation was provided to a variety of intramural and collaborative programs.

#### b. Electrical and Electronic Engineering

BEIB completed a substantial number of new designs for electrical and electronic apparatus for the NIH research programs; projects deserving special mention are summarized as follows:

Progress in clinical instrumentation was marked by further developments in two dimensional dynamic ultrasonic displays of physiological structures. Ultrasonic scanning was effectively extended to improve the quality of ophthalmological examinations and significant improvements were attained in measurements of blood flow rates. Others include: A new method for quantifying cortical metabolism as function of position via low light level TV fluoroscopy; a laser powered ophthalmological drill; electronic monitoring of culture growth; and several systems for multiplexing various modes of clinical information onto video displays.

In the field of laboratory instrumentation, noteworthy advances were made in cell separation technology; rapid-scan Fourier transform NMR; dual thermistor differential micro-calorimetry.

The patient electrical safety program was highlighted by the development of "second generation" test apparatus, new methods for scheduling and recording inspections, and more extensive consultation regarding equipment purchases.

#### c. Mechanical Engineering

Continued close collaboration with research and applications program principals throughout the NIH resulted in substantial developments in several areas. Mechanization and automation of routine laboratory procedures were extended and improved; large-scale media preparation operations and glassware processing were made more economical in terms of manpower and costs thus permitting reallocation of resources to more productive and challenging assignments.

Substantial advances were achieved in fundamental and applied research on concomitants of CNS trauma, particularly in examination of the relationship of electrical conduction in nerve fibers with mechanical shock; protection to clinical personnel handling radioactive material; new visual acuity tests; processing of electrophoretic preparations; combining the advantages of visual microscopy with those of electron microscopy; application of fluidic logic and control to the programming of reagent inputs to a rapid reaction stop-flow calorimeter.



A new family of instruments for use in eye surgery was generated. These include special surgical knives, a vitreous humor extractor, a unique foot control, a syringe drive, a sub-retinal fluid drainer, and new retinal suturing techniques. Two new devices for placement of electrodes in brain of man and of test animals are undergoing tests. Each of these advances the state of the art in specific areas.

Extensive consultation was provided to intramural, collaborative, and extramural programs.

d. Florence Agreement

BEIB is responsible for implementing NIH commitments related to the "Florence Agreement." Duties involve review of applications for duty-free entry of foreign manufactured scientific apparatus acquired by domestic nonprofit institutions, assessment of the suitability of equipment cited for intended applications, investigation of availability of domestically produced scientific equivalents, recommendations to the U.S. Department of Commerce for approval, disapproval, or resubmission; and providing pertinent technical advice to requesting agencies and the Department of Commerce. The Branch Chief serves as Chairman of the NIH Florence Agreement Committee which includes a number of NIH professionals who are expert in particular categories of instrumentation. The Executive Secretary, who must be thoroughly knowledgeable in modern scientific equipment, has become recognized as a reliable source of expert guidance, especially in the areas of transmission and scanning electron microscopy. Activities for FY 1975 are summarized as follows:

Number of applications received by NIH .....	610
Referred to other agencies .....	100
Processed by NIH .....	510
Processed independently by the Executive Secretary..	480
Processed with help of other Committee members .....	30
Recommendations for approval .....	340
Recommendations for disapproval .....	30
Recommendations for resubmission .....	140

3. Technical Advances

A CHIN ACTUATED REMOTE CONTROLLER manipulates a viewing microscope in three axes to enable full use of a surgeon's hands for ophthalmological procedures.

CONCOMITANTS OF NERVE TRAUMA are derived with a new apparatus that monitors compound action potential changes resulting from applied dynamic mechanical stresses.

A FLUIDIC LOGIC CONTROLLED SYSTEM transfers precise volumes of reagents within a chemical analyzer to improve the quality of kinetic reaction studies.

NMR SPECTROMETRY VIA RAPID SCAN FT TECHNIQUES is enhanced by automatic sequencing of fixed frequency pre-scan irradiation, homogeneity spoiling, and broad band rapid scan processes.

SCANNING ELECTRON MICROSCOPE VERSATILITY is substantially expanded with externally controlled accessories which provide three axis sample manipulation and direct optical viewing.

BACTERIAL GROWTH IN BLOOD CULTURE bottles is monitored more accurately and conveniently by measuring minute electrical impedance changes.

ELECTROPHORESIS GEL DESTAINING is accelerated by circulation of buffer through a charcoal bed.

AORTIC BALL VALVE PROSTHESIS INTEGRITY is non-invasively assessed with a coordinated radioisotopic and microphonic signal detection and data processing system.

RADIOACTIVE SERUM INFECTION with markedly improved safety is achieved with a novel tantalum-stainless steel syringe shield.

SYNCHRONOUS VIDEO DISPLAY of images and temporal signals substantially expedites interpretation and evaluation of cardiodynamic phenomena.

A VERSATILE TIME CODED DATA PLAYBACK TECHNIQUE using low speed magnetic tape recording is useful in epilepsy studies.

LOCALIZED QUANTITATIVE MEASUREMENT OF CORTICAL FLUORESCENCE, flow rate and oxygenation of blood adds new dimensions to the understanding of central nervous system metabolism.

A SYSTEM FOR IN VITRO STUDY OF CARDIAC MUSCLE HYPERTROPHY controls local ambient temperature and partial pressures of  $O_2$  and  $CO_2$ , supplies periodic isometric clamping and electrical stimulation, and optically determines muscle growth rate.

CONTAINERS UP TO ONE LITER ARE AUTOMATICALLY LABELED with pressure sensitive printed tags at a rate of 110 per minute in a mechanized glassware processing apparatus.

A MULTIPLEXED VIDEO MONITOR AND TAPE RECORDING SYSTEM helps to define the relationship between evoked pupillary response and CNS disorders.

A PROGRAMMABLE EXTERNAL CARDIAC PACEMAKER changes heart rate in prescribed temporal patterns as an aid to therapy.

AN INFANT HEAD MOTION MONITOR extends the versatility of a system used to study mother-infant behavior interactions.

A SELF CONTAINED PORTABLE VISUAL ACUITY TESTER implements the "illiterate E" test randomly to eliminate the effect of patient anticipation.

#### 4. Training

An effective professional and technical program was essential in maintaining high quality support and service. Fifty-seven employees participated in

116 academic, administrative, and technical courses. Thirteen (123 man-days) undertook formal university education and training courses. Thirteen (52 man-days) received specialized training on scientific equipment at manufacturers' facilities and at the NIH. Thirty-eight (165 man-days) attended various administrative, clerical, technical and scientific courses and training seminars. One employee attended Basic Adult Education at NIH sponsored by the Montgomery County School System and three employees were enrolled in the Upward Mobility College taking a total of 25 quarters of college-level courses.

#### D. Program Plans

Fiscal 1975 was distinguished by the refinement and extension of concepts, methods and devices conceived in previous years. Several promising new avenues of investigation were opened in fundamental research and engineering applications. The expectation of constraints on personnel and materiel for the coming year requires careful consideration of priorities and utilization of available resources. Modified methods for maximally satisfying the needs of the NIH program including, perhaps, more extensive use of contractors is anticipated. Reorientation of duties and functions within the Branch must be explored.

1. Considerable emphasis will be placed on innovating, improving and extending engineering applications for the benefit of research and clinical practice, especially in the areas of:

- a. Optimization of chemotherapeutic processes.
- b. Detection and analysis of trace elements and their role in toxicology, diagnosis, and treatment.
- c. Elucidation of the interaction between implanted artificial devices and the living environment.
- d. Improved non-invasive physiological measurements and anatomical imaging.
- e. Explication of the chemical, electrical and mechanical concomitants of physiological phenomena associated with muscle, nerve, and blood.
- f. Automated materiel and information processing systems.
- g. Apparatus and methods for protection of personnel from hazards in laboratories and clinics.

2. Expansion of the Scientific Equipment Rental Program and increased operational efficiency.

3. More extensive use of private sector capabilities for procurement of services via contract.

4. Incorporation of Branch financial management functions within the forthcoming NIH Material Management and Common Accounting Systems to improve responsiveness and economy of operations.

## E. Publications and Patents

### 1. Publications

Bender, R.A. and Dedrick, R.L.: Cytokinetic aspects of clinical drug resistance. Cancer. Chemother. Rep. (In press)

Berger, R.L., Friauf, W.S., Cascio, H.E.: A low-noise thermistor bridge for use in calorimetry. Clin. Chem. 20: 1009-1012, 1974.

Bischoff, K.B. and Dedrick, R.L.: Addendum to "Critical evaluation of use of effective protein fractions in developing pharmacokinetic models for drug distribution." Shen, D. and Gibaldi, M.: J. Pharm. Sci. 63: 1702-1703, 1974.

Boretos, J.W. and Brown, J.W.: Materials and design considerations for improved apical aortic anastomosis. In Brighton, J.A. and Goldstein, S.R. (eds.): Advances in Bioengineering, New York, NY, American Society of Mechanical Engineers, 1974, pp. 165-166.

\_\_\_\_\_: Silicones. In Polymers in Medicine and Surgery, Proceedings of a Symposium, 1974, Morristown, New Jersey. Kronenthal, D. and Oser, Z. (eds.) Plenum Polymer and Science Technology Series, Plenum Press. (In press)

\_\_\_\_\_, Pierce, W.S., Baier, R.E., LeRoy, A.F., and Donachy, H.J.: Surface and bulk characteristics of a polyether urethane for artificial heart. J. Biomed. Mater. Res. (In press)

Brighton, J.B. and Goldstein, S.R. (eds.): Advances in Bioengineering, New York, NY, American Society of Mechanical Engineers, 1974, 190 pp.

Cohen, J.S., Bradley, R.B. and Clem, T.R.: pH dependence of the <sup>13</sup>C spin-lattice relaxation rate of the carboxyl carbon of acetic acid. J. Am. Chem. Soc. 97: 908-909, 1975.

Cohen, S.C., Gabelnick, H.L., Johnson, R.K. and Goldin, A.: Effects of cyclophosphamide and adriamycin on the healing of surgical wounds in mice. Cancer (In press)

\_\_\_\_\_, \_\_\_\_\_, \_\_\_\_\_, and \_\_\_\_\_: Effects of antineoplastic agents on wound healing in mice. Surgery (In press)

Dedrick, R.L.: Book Review: Transport Phenomena and Living Systems: Biomedical Applications of Momentum and Mass Transfer, by E.N. Lightfoot. Amer. Inst. of Chem. Engineers J. 20: 829, 1974.

\_\_\_\_\_: Animal scale-up. In Teorell, T., Dedrick, R.L. and Condliffe, P.G. (eds.) Pharmacology and Pharmacokinetics, Plenum Press, New York, NY, 1974, pp 117-144.

\_\_\_\_\_: Pharmacokinetic and pharmacodynamic considerations for chronic hemodialysis. Kidney International 7: S7-15, 1975.



\_\_\_\_\_, Zaharko, D.S., Lutz, R.J. and Drake, J.C.: Device for controlled drug release-application to methotrexate infusion in mice. Biochem. Pharmacol. 23: 2457-2461, 1974.

\_\_\_\_\_, \_\_\_\_\_, Bender, R.A., Bleyer, W.A. and Lutz, R.J.: Pharmacokinetic considerations on resistance to anti-cancer drugs. Cancer Chemother. Rep. (In press)

Dvorak, J.A., Schuette, W.H. and Whitehouse, W.C.: A simple method for the quantification of geometric parameters of microscopic objects. J. Microsc. 102: 71-78, 1974.

Friauf, W.S.: Test equipment for hospital safety programs. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 496.

Gennarelli, T.A. and Thibault, L.E.: Functional response of the central nervous system to controlled inertial loading. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 175.

Goldstein, S.R.: A servo-force balance isometric muscle force transducer. J. Appl. Physiol. 37: 134-137, 1974.

\_\_\_\_\_, Schmidt, E.M., Bierley, F.L. and Bak, M.: Atraumatic electrical recording from the exposed pulsating human cerebral cortex--a new mechanism. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 224. Also in ASME Advances in Bioengineering, 1974, pp. 52-54.

\_\_\_\_\_, \_\_\_\_\_, \_\_\_\_\_, and \_\_\_\_\_: A gas bearing mechanism for stable electrical recording from individual neurons in pulsating human cerebral cortex. Trans. ASME, J. Dynamic Systems, Measurement, Control. (In press).

Griffith, J.M. and Henry, W.L.: Switched gain: simplifies ultrasonic measurement of cardiac wall thickness. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 264.

\_\_\_\_\_ and \_\_\_\_\_: A sector scanner for real-time, two-dimensional echocardiography. Circulation XLIX: 1147-1152, 1974.

\_\_\_\_\_ and \_\_\_\_\_: Switched gain: a technique for simplifying ultrasonic measurement of cardiac wall thickness. IEEE Trans. BME (In press)

Gross, J.F. and Dedrick, R.L.: Macroscopic pharmacokinetics and cancer chemotherapy. In Proceedings of Joint Meeting of Verfahrenstechnische Gesellschaft in Verein Duetscher Ingenieure and AICHe, 1974, Munich, Germany. Dusseldorf, West Germany, AICHe-GVC, 1974, paper F4-5.

Henry, W.L., Epstein, S.E., Griffith, J.M., Goldstein, R.E. and Redwood, D.R.: Effect of prolonged space flight on cardiac function and dimensions. In Proceedings of the Skylab Life Sciences Symposium, August 27-29, 1974, Houston, Texas. The Lyndon B. Johnson Space Center, Houston, Texas, 1974, pp 711-721.

\_\_\_\_\_, Griffith, J.M., Michaelis, L.L., McIntosh, C.L., Morrow, A.G., and Epstein, S.E.: Measurement of mitral orifice area in patients with mitral valve disease by real-time, two-dimensional echocardiography. Circulation 51: 827-831, 1975.

\_\_\_\_\_, Clark, C.E., Griffith, J.M. and Epstein, S.E.: Mechanism of left ventricular outflow obstruction in patients with obstructive asymmetric septal hypertrophy (Idiopathic hypertrophic subaortic stenosis.) Am. J. Cardiol. 35: 337-345, 1975.

\_\_\_\_\_, Maron, B.J., Griffith, J.M., Redwood, D.R. and Epstein, S.E.: Differential diagnosis of anomalies of the great arteries by real-time two-dimensional echocardiography. Circulation 51: 283-291, 1975.

Kump, W.R. and Dehn, W.R.: Fabrication techniques for multichannel micro-electrodes. Fusion, May 1975, pp 9-10.

LeRoy, A.F.: Health consequences of environmental controls: Impact of mobile emissions control. Interactions of platinum-metals and their complexes in biological systems. Environ. Health Perspect. (In press)

\_\_\_\_\_ (ed.): Trace contaminants in the environment. Chemical Engineering Progress Symposium Series (In press)

\_\_\_\_\_: Introduction. In LeRoy, A.F. (ed.): Trace contaminants in the environment. Chemical Engineering Progress Symposium Series (In press)

Levy, D.M., Metz, H.D., Friauf, W.S. and Johnson, R.K.: An automatic cell growth and biochemical analysis system. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 476.

Lewis, D.V. and Schuette, W.H.: NADH fluorescence and  $[K^+]_o$  changes during hippocampal electrical stimulation. J. Neurophysiol. 38: 405-417, 1975.

\_\_\_\_\_, O'Connor, M.J. and Schuette, W.H.: Oxidative metabolism during recurrent seizures in the penicillin treated hippocampus. Electroencephalogr. Clin. Neurophysiol. 36: 347-356, 1974.

Lutz, R.J., Cannon, J.N., Munroe, R.E.: Shear stress measurements in model arteries during steady and pulsatile flow. In Nerem, R.M. (ed.): Fluid Dynamic Aspects of Arterial Disease. Proceedings from a Specialists Meeting on Fluid Dynamic Aspects of Arterial Disease, September 19-20, 1974, Columbus, Ohio, pp 5-8.

\_\_\_\_\_, \_\_\_\_\_, Fletcher, J.E. and Fry, D.L.: The measurement of wall shear stress in model arteries by an electrochemical technique. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 279.

\_\_\_\_\_, Dedrick, R.L., Straw, J.A., Hart, M.M., Klubes, P. and Zaharko, D.S.: The kinetics of methotrexate distribution in spontaneous canine lymphosarcoma. J. Pharmacokinet. Biopharm. (In press)

Myerowitz, P.D., Griffith, J.M., Roberts, A.J., Harrison, L.H., Henry, W.L., and McIntosh, C.L.: Long-term canine model for echocardiography. Am. J. Cardiol. 34: 72-74, 1974.

Olson, H.M., Young, D.M., Prieur, D.J., LeRoy, A.F. and Reagan, R.L.: Electrolyte and morphological alterations of myocardium in adriamycin-treated rabbits. Am. J. Pathol. 77: 439-454, 1974.

\_\_\_\_\_, Rosenoff, S.H., Reagan, R.L., Munroe, R.E., LeRoy, A.F., Young, R.C., Young, D.M.: Ultrastructural alterations of the myocardium and biochemical correlates in mice with adriamycin administration. Cancer Res. (In press)

Peterson, J.I., Tipton, H. and Chrambach, A.: A gel slicer for transverse sectioning of polyacrylamide gels. Anal. Biochem. 62: 274-280, 1974.

Redwood, D.R., Henry, W.L., Goldstein, S.R. and Smith, E.R.: Design and function of a mechanical assembly for recording echocardiograms during upright exercise. Cardiovasc. Res. 9: 145-149, 1975.

Rhee, S.G., Greifner, M.I. and Chock, P.B.: ATP determination by stopped-flow method. Anal. Biochem. (In press)

Schuette, W.H., Grauer, L.E., Whitehouse, W.C., Itscoitz, S.B. and Redwood, D.R.: Measurement of ventricular ejection fraction in man utilizing roentgen videodensitometry. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 438.

\_\_\_\_\_, Whitehouse, W.C., Lewis, D.V., O'Connor, M. and Van Buren, J.M.: A television fluorometer for monitoring oxidative metabolism in intact tissue. Med. Instrum. 8: 331-333, 1974.

Straw, J.A., Hart, M.M., Klubes, P., Zaharko, D.S. and Dedrick, R.L.: Distribution of anticancer agents in spontaneous animal tumors. I. Regional blood flow and methotrexate distribution in canine lymphosarcoma. J. Natl. Cancer Inst. 52: 1327-1331, 1974.

Teorell, T., Dedrick, R.L. and Condliffe, R.G. (eds.): Pharmacology and Pharmacokinetics, Plenum Press, New York, NY, 1974, 388 pp.

Thibault, L.E., Gennarelli, T.A., Tipton, H.W. and Carpenter, D.O.: The physiological response of isolated nerve tissue to dynamic mechanical loads.

In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 176.

Thompson, E.J., Griffith, J.M., Schoenberg, D.G. and Nirenberg, M.W.: An improved method for extracellular recording of action potentials from single cultured neuroblastoma cells. Med. Biol. Eng. 104-106, January 1975.

Vurek, G.G., Warnock, D.G. and Corsey, R.: Measurement of picomole amounts of carbon dioxide by calorimetry. Anal. Chem. 47: 765-767, 1975.

Wasylishen, R.E., Clem, T.R. and Becker, E.D.: Nuclear magnetic resonance chemical shifts of some monosubstituted isothiazoles. Can. J. Chem. 53: 596-603, 1975.

Zaharko, D.S. and Dedrick, R.L.: Pharmacokinetic models for antineoplastic agents. In Sartorelli, A.C. and Johns, D.G. (eds.): Antineoplastic and Immunosuppression Agents I. Springer-Verlag, Berlin, 1974, pp. 220-228.

\_\_\_\_\_, \_\_\_\_\_, Peale, A.L., Drake, J.C. and Lutz, R.J.: Relative toxicity of methotrexate in several tissues of mice bearing lewis lung carcinoma. J. Pharmacol. Exp. Ther. 189: 585-592, 1974.

## 2. Patents

Boretos, J.W.: "Device for treating sub-ungual hematoma." U.S. Patent No. 3,766,923 (October 23, 1973).

Goldstein, S.R.: "Electrode insertion device for neuroelectrical recordings." U.S. Patent No. 3,841,310 (October 15, 1974).

Knazek, R.A., Gullino, P.M., Dedrick, R.L. and Kidwell, W.R.: "Cell culture on semipermeable tubular membranes." U.S. Patent No. 3,821,087 (June 29, 1974)

Peterson, J.I., Friauf, W.S. and Leighton, S.: "A high-precision fluorometer for measuring enzymatic substrates in tissues." U.S. Patent No. 3,854,050 (December 10, 1970).

Schuette, W.H.: "Modulated sine wave flowmeter." U.S. Patent No. 3,815,582 (June 11, 1974).



III INDIVIDUAL PROJECT REPORTS

Project No. Z01 RS 00001-07 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1974 through June 30, 1975

Project Title: Pharmacokinetics

Previous Serial Number: DRS-BEIB-1

Principal Investigator: Robert L. Dedrick

Other Investigators: Daniel S. Zaharko, Richard A. Bender, Anthony M. Guarino, Robert J. Lutz, André F. LeRoy, Kenneth B. Bischoff, Marshall Anderson, Bruce Chabner, W. Archie Bleyer

Cooperating Units: LCHPH-NCI, LT-NCI, PB-NIEHS, AK-CU Program NIAMDD, University of Washington, M-NCI

Man Years:

Total:	3.0
Professional:	2.0
Other:	1.0

Project Description:

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants and endogenous metabolites in animals and man to:

- (1) Account for species differences in drug distribution.
- (2) Provide rational bases for extrapolation of toxicity from animals to man.
- (3) In conjunction with pharmacodynamics, provide a basis for optimization of cancer chemotherapy and chronic hemodialysis.
- (4) Enable rational transfer of in vitro thermodynamic and kinetic data to in vivo cases.
- (5) Predict effective dose schedules of anti-cancer drugs in individual patients.

Methods Employed: Mathematical models are developed from physicochemical, physiological and anatomical information and the principles of chemical reaction engineering. Resulting differential equations sets are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

## Major Findings:

- (1) Methotrexate distribution in spontaneous canine lymphosarcoma has been modeled as a saturable transport process with strong intracellular binding to dihydrofolate reductase and weak binding to cell membranes or extracellular tumor components.
- (2) A pharmacokinetic model, originally developed on the basis of extensive studies in mice, has been used successfully to predict methotrexate priming doses and infusion rates required to achieve selected plasma concentrations in individual patients.
- (3) Tumor perfusion, membrane transport, intracellular enzyme levels and enzyme synthesis rate have been illustrated and placed in quantitative perspective by a discussion of the pharmacokinetics and pharmacodynamics of methotrexate. This provides an operational basis for examination of drug resistance.
- (4) Filterability of platinum administered as cis-dichlorodiammine platinum (II) decreases during incubation with dog plasma in vitro. This appears to correlate with a decrease in kidney clearance in vivo and suggests that one or more chemical reactions occur which may influence distribution, disposition, and biological effect.

Significance: Drugs and other chemicals are tested for effect in animals, and the extrapolation to man is a subject of serious concern. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with particular attention to pharmacodynamic and cytotoxic events. Increased clinical emphasis through support of high-dose methotrexate protocols and other attempts to overcome drug resistance.

Keyword Descriptors: Pharmacokinetics, methotrexate, polychlorinated biphenyls, mathematical modeling, drug resistance, cancer chemotherapy, cis-dichlorodiammine platinum (II).

Honors and Awards: Food, Pharmaceutical and Bioengineering Division Award of American Institute of Chemical Engineers to R.L. Dedrick.

## Publications:

Teorell, T., Dedrick, R.L. and Condliff, P.G. (Eds.): Pharmacology and Pharmacokinetics. New York, Plenum Press, 1974, 388 pp.

Dedrick, R.L.: Animal Scale-Up. In Teorell, T., Dedrick, R.L. and Condliffe, P.G. (Eds.): Pharmacology and Pharmacokinetics, New York, Plenum Press, 1974, pp. 117-144.

\_\_\_\_\_, Zaharko, D.S., Lutz, R.J. and Drake, J.C.: Device for Controlled Drug Release: Application to Methotrexate Infusion in Mice. Biochem. Pharmacol. 23: 2457-2461, 1974.

Straw, J.A., Hart, M.M., Klubes, P., Zaharko, D.S. and Dedrick, R.L.: Distribution of Anticancer Agents in Spontaneous Animal Tumors. I. Regional Blood Flow and Methotrexate distribution in Canine Lymphosarcoma. J. Nat. Cancer Inst. 52, 1327-1331, 1974.

Zaharko, D.S. and Dedrick, R.L.: Pharmacokinetic Models: Application to Antineoplastic Agents. In Sartorelli, A.C. and Johns, D.G.(Eds.): Handbook of Experimental Pharmacology XXXVIII/I, Berlin, Springer Verlag, 1974, pp. 220-228.

\_\_\_\_\_, \_\_\_\_\_, Peale, A.L., Drake, J.C. and Lutz, R.J.: Relative Toxicity of Methotrexate in Several Tissues of Mice Bearing Lewis Lung Carcinoma. J. Pharmacol. Exp. Therap. 189: 585-592, 1974.

Gross, J.F. and Dedrick, R.L.: Macroscopic Pharmacokinetics and Cancer Chemotherapy. Proc. Joint Meeting Gesellschaft Verfahrenstechnik und Chemieingenieurwesen (GVC) and American Institute of Chemical Engineers (AIChE), Munich, Germany, 1974, Paper F4-5, 10 pp.

Bischoff, K.B. and Dedrick, R.L.: Addendum to Shen, D. and Gibaldi, M.: Critical Evaluation of Use of Effective Protein Fractions in Developing Pharmacokinetic Models for Drug Distribution. J. Pharm. Sci. 63: 1702-1703, 1974.

Dedrick, R.L.: Pharmacokinetic and Pharmacodynamic Considerations for Chronic Hemodialysis. Kidney International 7 (Suppl. 2), S-7-15, 1975.

\_\_\_\_\_, Zaharko, D.S., Bender, R.A., Bleyer, W.A. and Lutz, R.J.: Pharmacokinetic Considerations on Resistance to Anti-Cancer Drugs. Cancer Chemotherapy Rep. (In Press).

Bender, R.A. and Dedrick, R.L.: Cytokinetic Aspects of Clinical Drug Resistance. Cancer Chemotherapy Rep. (In Press)

Lutz, R.J., Dedrick, R.L., Straw, J.A., Hart, M.M., Klubes, P. and Zaharko, D.S.: The Kinetics of Methotrexate Distribution in Spontaneous Canine Lymphosarcoma. J. Pharmacokinet. Biopharm. (In Press).

Bischoff, K.B.: Pharmacokinetics and Cancer Chemotherapy. In Teorell, T., Dedrick, R.L. and Condliffe, P.G. (Eds.): Pharmacology and Pharmacokinetics, New York, Plenum Press, 1974, pp. 351-366.

\_\_\_\_\_: Some Fundamental Considerations in Applications of Pharmacokinetics to Cancer Chemotherapy. Cancer Chemotherapy Rep. (In Press).

Project No. Z01 RS 00002-10 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Implant Device Development

Previous Serial Number: DRS-BEIB-4

Principal Investigator: John W. Boretos

Other Investigators: William S. Pierce, Robert Poirier, James W. Prescott,  
C. Kollarits, M. Fisherman, John W. Brown, Robert Baier,  
Robert L. Dedrick, Robert J. Lutz

Cooperating Units: SB-NHLI, GD-NICHD, Pennsylvania State University, CB-NEI,  
Calspan Corp.

Man Years:

Total:	1.8
Professional:	1.5
Others:	0.3

Project Description:

Objectives: Elucidate the interaction of polymers used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic polymer composition is carefully controlled and modification of cross-linking systems is employed. Rheological properties are studied as a function of cross-linking. Implants are examined after removal for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Observations include SEM, infrared spectroscopy, contact angle measurements, energy dispersive x-ray analysis and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied in vitro in test apparatus.

Major Findings: Ten heart assist devices with segmented polyurethane blood contacting surfaces were implanted in calves for up to 35 weeks. No lipid absorption was observed; physical strength remained stable; surfaces developed a biocompatible layer of protein. Six additional assist devices have been implanted with similar results; two total heart implants have been achieved.



A series of ventricular-aortic by-pass devices functioned satisfactorily for periods up to 17 weeks in dogs with negligible blood damage. Clinical trials are now being planned.

Six segmented polyurethane covered polypropylene poppets housed in standard "Starr-Edwards 3M" cages have been implanted in calves. One was electively removed after one year; no obvious physical or chemical changes occurred and there was no evidence of injury to the animal.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart assist devices, vascular implants, and subcutaneous uses.

Proposed Course: (1) Extend experimental studies to further characterize the surface and bulk properties of polyether urethanes and more specifically determine its interactions with blood and subcutaneous tissue.

(2) Study new designs of tricuspid heart valves for acute and chronic use.

(3) Study new designs of drains to be used in the eye to treat glaucoma.

Keyword Descriptors: Polymers, implants, heart valves, heart pumps, glaucoma drains.

Honors and Awards: None

Publications:

Boretos, J.W., Pierce, W.S., Baier, R.E., LeRoy, A.F., and Donachy, H.J.: Surface and Bulk Characteristics of a Polyether Urethane for Artificial Heart. J. Biomed. Mater. Res. (in press).

Boretos, J.W. and Brown, J.W.: Materials and Design Characteristics for Improved Apical Aortic Anastomosis. In 1974 ASME Advances in Bioengineering. Brighton, J.A. and Goldstein, S.R. (eds.) American Society of Mechanical Engineers.

Boretos, J.W.: Silicones. In Polymers in Medicine and Surgery, Proceedings of a Symposium, 1974, Morristown, New Jersey. Kronenthal, D. and Oser, Z. (eds.), Plenum Polymer and Science Technology Series, Plenum Press (in press).

Boretos, J.W.: Polymer Considerations for Electronic Implants. In Ray, C.D. (ed.) Medical Engineering, Year Book Medical Publishers, Inc., Chicago, IL, 1974, pp 1120-1123.

Boretos, J.W.: Machining of Plastics. In Ray, C.D. (ed.), Medical Engineering, Year Book Medical Publishers, Inc., Chicago, IL, 1974, pp. 1173-1181.

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Trace Element Analysis in Biological Materials

Previous Serial Number: DRS-BEIB-2

Principal Investigators: André F. LeRoy

Other Investigators: H.M. Olson, A.M. Guarino, R.L. Dedrick, C. Litterst,  
T.E. Gram, G.P. Canellos

Cooperating Units: LT-NCI, M-NCI

Man Years:

Total:	2.0
Professional:	1.6
Others:	0.4

Project Description:

Objectives: Enhance analysis and identification of metal complexes in biological materials. Improve analytical methods with detection limits on the order of nanograms to picograms in milligram samples. Emphasize analysis of platinum, gallium, calcium and magnesium compounds as they relate to diagnosis and chemotherapy.

Methods Employed: Flameless atomic absorption spectrophotometry for analysis of specific elements. Chemical agents are used to promote release of elements from the biological matrix more smoothly and completely. Solvent extraction may be very useful for many applications. Electronic control of the temperature program for combustion allows materials with different combustion characteristics to be analyzed.

Electrophoresis to fractionate proteins with subsequent determination of metal species among fractions. In some cases, ultrafiltration is required to concentrate proteins enough to permit detection of metals.

Major Findings: Sensitivity of platinum determination is approximately one nanogram. Urine and plasma samples from dogs treated with cis-dichlorodiamine platinum have been directly analyzed as a function of time. More than half of platinum administered appears in the urine within about two hours; the remainder is released in the urine much more slowly. Samples of various tissues from treated dogs have been analyzed after acid digestion. The results indicate that loss of platinum taken up in tissue is very slow.

Direct analysis of gallium has given erratic results to date.

Significance: Quantitation, identification and characterization of metal species at trace levels in biological tissue is important in biochemical research and environmental toxicology. Characterization of such compounds in tissues and body fluids can help identify drug action and suggest other potentially useful compounds. Methods under development offer an alternative to administering radiolabeled substances to human subjects.

Proposed Course: Extend applicability of direct combustion techniques to more tissue types by use of suitable time-temperature relationships; try to minimize need for pretreatment. Complete analyses required for pharmacokinetic modeling. Perform referee analyses for metals using neutron activation analysis where applicable. Improve analysis for gallium.

Keyword Descriptors: Trace-element analysis, biological tissues and fluids, atomic absorption spectrophotometry.

Honors and Awards: None

Publications:

LeRoy, A.F.: Interactions of Platinum-Metals and Their Complexes in Biological Systems. Environ. Health Perspect. (in press.)

Olson, H.M., Rosenoff, S.H., Reagan, R.L., Munroe, B., LeRoy, A.F., Young, R.C., Young, D.M.: Ultrastructural Alterations of the Myocardium and Biochemical Correlates in Mice with Adriamycin Administration. Cancer Res. (in press.)

Olson, H.M., Young, D.M., Prieur, D.J., LeRoy, A.J., Reagan, R.L.: Electrolyte and Morphologic Alterations of Myocardium in Adriamycin-Treated Rabbits. Am. J. Pathol. 77: 439-450, 1974.

Project No. Z01 RS 00004-05 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: The Role of Fluid Dynamics and Mass Transfer in Development of Atherosclerosis

Previous Serial Number: DRS-BEIB-3

Principal Investigators: Robert J. Lutz, Joseph N. Cannon

Other Investigators: Donald L. Fry, Robert L. Dedrick, Kenneth B. Bischoff

Cooperating Units: OD-IR-NHLI, Howard University

Man Years:

Total:	1.2
Professional:	0.8
Other:	0.4

Project Description:

Objectives: Measure shear stress on the inner wall of simulated arteries during steady and pulsatile flow and correlate data with localization of atherosclerosis as found in experimental animals. Visualize flow patterns in the three-dimensional geometry of arterial branches. Measure the effects of shear on the transport rate of macromolecules through simulated and real arterial endothelium.

Methods Employed: An electrochemical technique is used, based on an oxidation-reduction reaction at electrodes implanted at a fluid-solid interface, which determines mass transfer rates of redox ions. Velocity gradients at the wall (shear rate) are calculated from mass transfer rates with suitable boundary layer equations.

Flow visualization can be achieved in a transparent cast of a canine artery using dye injection techniques and/or cinematography of latex microspheres.

Major Findings: In the arterial model, sharp shear peaks exist near the flow divider tips of branches; shear rate rises as flow enters smaller branches where velocity profiles are redeveloping. Shear drops suddenly just distal to the flow divider tips resulting in flow separation and flow reversal during pulsations. The intricate three-dimensional geometry of the arterial tree and branching of the flow from the main channel are responsible for flow pattern characteristics. Regions of high shear and regions of disturbed flow patterns correlate with areas of increased plaque localization.

Significance: Elucidation of the role of hemodynamics and mass transfer in the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease

Proposed Course: Verify electrochemical techniques experimentally and by computer simulation for measuring pulsatile shear stresses. Fabricate more realistic arterial models which include wall distensibility, and determine shear rate patterns. Devise mechanical models of the phospholipid membrane of arterial endothelial cells and determine the effect of shear on transport of macromolecules across these artificial membranes.

Keyword Descriptors: Atherosclerosis, electrochemical shear measurement, arterial models, arterial fluid dynamics

Honors and Awards: None

Publications:

Lutz, R.J., Cannon, J.N., Fletcher, J.E., and Fry, D.L.: The Measurement of Wall Shear Stress in Model Arteries by an Electrochemical Technique. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 27.

Lutz, R.J., Cannon, J.N., Munroe, R.E.: Shear Stress Measurements in Model Arteries During Steady and Pulsatile Flow. In Nerem, R.M. (Ed.): Fluid Dynamic Aspects of Arterial Disease. Proceedings From a Specialists Meeting on Fluid Dynamic Aspects of Arterial Disease, Columbus, Ohio, September 19-20, 1974, pp. 5-8.

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1974 through June 30, 1975

Project Title: Multicomponent Plastics in Biomedical Use

Previous Serial Number: DRS-BEIB-5

Principal Investigator: Henry L. Gabelnick

Other Investigator: Margaret L. Wehling

Cooperating Units: None

Man Years:

Total:	0.6
Professional:	0.3
Other:	0.3

Project Description:

Objectives: Extend definition of the interaction of plastic systems with the biological environment, emphasizing the kinetics of additive elution from polymers and absorption of body constituents.

Methods Employed: Determination of elution rate of migrating species via quantitative analytical techniques. Parameters under investigation include fluid composition and flow conditions.

Major Findings: Refined analytical techniques enable evaluation of the di-2-ethylhexylphthalate-polyvinyl chloride system exposed to a soybean emulsion "pseudo-serum."

Desorption of phthalate from surgical grade polyvinyl tubing (3/16" I.D.) was independent of flow rate over the range 100 to 300 ml/min. However, the rate of uptake of phthalate by the pseudo-serum increased by a factor of two when the lipid concentration was increased from 100 to 300 mg%.

Proposed Course: Project terminated in December 1974 due to departure of the principal investigator.

Keyword Descriptors: Phthalates, plasticizers elution, vinyl tubing, desorption kinetics

Honors and Awards: None

Publications: None



Project No. Z01 RS 00005-03 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Chemical Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Thermomicrography

Previous Serial Number: None

Principal Investigators: John I. Peterson

Other Investigators: Robert L. Bowman

Cooperating Units: LTD-NHLI

Man Years:

Total:	1.3
Professional:	0.8
Other:	0.5

Project Description:

Objectives: Develop a method for microscopic observation of biological cells by their thermal effects.

Methods Employed: Investigation of the possible use of the optical-thermal properties of the cholesteric mesophase ("liquid crystals").

Major Findings: The well-known and previously investigated properties of cholesteric esters have been based on materials of undocumented and probably low purity. The accepted theoretical model for their behavior is untenable from the chemical point of view. The investigation of highly purified material shows behavior which is different and possibly more useful than previously observed, as well as being divergent from that expected.

Significance: A technic of microthermography would be useful for cell calorimetry and other energy studies on an individual cell basis, and could provide a possible route to facilitation of screening studies involving various kinds of cellular reactions.

Proposed Course: Verification of conclusions derived to date and extension through continued investigation.

Keyword Descriptors: Thermography, liquid crystals, purification, cholesteric esters.

Honors and Awards: None

Publications: None

Project No. Z01 RS 00007-01 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

Previous Serial Number: DRS-BEIB-7

Principal Investigators: William H. Schuette, Darrell V. Lewis

Cooperating Units: EEG-NINDS

Man Years:

Total:	2.0
Professional:	1.5
Others:	0.5

Project Description:

Objectives: (1) Develop and apply new and improved techniques for analyzing oxidative metabolism of the cat brain and correlating these results to simultaneous extracellular potassium kinetic measurements.

(2) Determine the  $Q_{10}$  of potassium kinetics in the cat hippocampus.

(3) Validate oxidative metabolism measurements obtained by NADH fluorescence techniques with direct measurement of cortical oxygen consumption.

Methods Employed: NADH fluorescence measurements are made with a unique two-channel fluorometer.

$Q_{10}$  measurements are made by cooling the brain with an "Elliott's B" solution drip while measuring local temperature with a thermistor. Potassium kinetics are measured with a potassium sensitive microelectrode following electrical stimulation.

Cortical oxygen consumption is determined from the combination of oximetry and flow of blood drained from the sagittal sinus of cats.

Major Findings: (1) Clearance of potassium following stimulation of the brain is an exponential process.



(2) The  $Q_{10}$  for this clearance is approximately 2.1.

(3) A linear relationship exists between the amount of potassium released following a stimulus to the brain and the time integral of the NADH fluorescence signal.

(4) NADH fluorescence signals appear to be related to direct oxygen consumption measurements.

Significance: Evidence for potassium clearance being an active process has been reinforced.

The utility of NADH fluorescence as an indicator of oxidative metabolism has been demonstrated.

Proposed Course: Refinement and extension of work done to date.

Keyword Descriptors: NADH, fluorescence, potassium, kinetics, oximetry

Honors and Awards: None

Publications:

1. Lewis, D.V., O'Connor, M.J. and Schuette, W.H.: Oxidative Metabolism During Recurrent Seizures in the Penicillin-Treated Hippocampus. Electroencephalogr. Clin Neurophysiol. 36: 347-356, 1974.

2. Schuette, W.H., Whitehouse, W.C., Lewis, D.V., O'Connor, M.J. and Van Buren, J.M.: A Television Fluorometer for Monitoring Oxidative Metabolism in Intact Tissue. Med. Instrum. 8: 331-333, 1974.

3. Lewis, D.V. and Schuette, W.H.: NADH Fluorescence and  $[K^+]_o$  Changes During Hippocampal Electrical Stimulation. J. Neurophysiol. 38: 405-417, 1975.

Project No. Z01 RS 00008-03 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Diagnostic Ultrasound

Previous Serial Number: DRS-BEIB-8

Principal Investigators: James M. Griffith, Walter L. Henry, William R. Brody, Steven Charles

Other Investigators: David Myerowitz, Barry J. Maron, Stephen E. Epstein

Cooperating Units: CB-IR-NHLI, SU-IR-NHLI, IR-NEI

Man Years:

Total:	3.5
Professional:	2.0
Others:	1.5

Project Description:

Objectives: (1) Noninvasively obtain dynamic images and measurements of cardiac structure and function and assess for diagnostic and therapeutic purposes.

(2) Noninvasively obtain images and measurements of ophthalmic structure and assess for diagnostic and therapeutic purposes.

(3) Noninvasively obtain dynamic measurements of blood flow in circulatory vessels.

Methods Employed: A previously reported real-time, two-dimensional sector scanner was refined and used effectively in several new research applications.

The sector scanner technique was extended to ophthalmological applications.

Principles of high resolution radar and communication theory are being applied to doppler flowmeter design for improved resolution.

A moving-trace monitor system was developed which allows two seconds of EKG to be recorded on each frame of real-time two-dimensional echogram.

Major Findings:

- (1) Mitral valve orifice area can be accurately measured by real-time two-dimensional echocardiography.
- (2) Two-dimensional echocardiography is a significant new tool for the differential diagnosis of anomalies of the great arteries.
- (3) Mechanical sector scanning in real time is applicable to ophthalmic scanning; this considerably reduces examination time.

Significance: Safe noninvasive methods for making quantitative and qualitative physiologic measurements are of substantial value for research and diagnostic purposes.

Proposed Course: The doppler flowmeter design will be improved so that useful velocity and range resolution are obtained. Then it may be possible to combine a flowmeter and a sector scanner so that real-time two-dimensional imaging is available simultaneously with flow measurement.

Keyword Descriptors: Ultrasound, Pulse Echo, doppler

Honors and Awards: None

Publications:

1. Griffith, J.M. and Henry, W.L. A Sector Scanner for Real Time Two-Dimensional Echocardiography. Circulation, XLIX: 1147-1152, 1974.
2. Myerowitz, P.D., Griffith, J.M., Roberts, A.J., Harrison, L.H., Henry, W.L., and McIntosh, C.L. Long-Term Canine Model for Echocardiography. Am. J. Cardiol. 34: 72-74, 1974.
3. Griffith, J.M. and Henry, W.L. Switched Gain: Simplifies Ultrasonic Measurement of Cardiac Wall Thickness. In Proceedings of the 27th Annual on Engineering in Medicine and Biology 1974, Philadelphia, Pennsylvania, Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 264.
4. Myerowitz, P.D., Brown, J.W., Harrison, L.H., Griffith, J.M., Henry, W.L. and McIntosh, C.L. A Comparison of Simultaneous Echocardiographic and Electromagnetic Flowmeter Determination of Stroke Volume. Supplement III to Circulation, Vols. 49 and 50, October 1974.
5. Henry, W.L., Griffith, J.M., Michaelis, L.L., McIntosh, C.L., Morrow, A.G., and Epstein, S.E. Quantitation of the Mitral Orifice Area by Real-Time Two-Dimensional Echocardiography. Supplement III to Circulation, Vols. 49 and 50, October 1974.
6. \_\_\_\_\_, Epstein, S.E., Griffith, J.M., Goldstein, R.E., Redwood, D.R. Effect of Prolonged Space Flight on Cardiac Function and Dimensions. Am. J. Cardiol. 35: 143, 1975.

7. Griffith, J.M. and Henry, W.L. A Moving-Trace Monitor for Video Systems. Med. Instrum. 9: 73, 1975.
8. Henry, W.L., Maron, B.J., Griffith, J.M., Redwood, D.R., and Epstein, S.E. Differential Diagnosis of Anomalies of the Great Arteries by Real-Time Two-Dimensional Echocardiography. Circulation 51: 283-291, 1975.
9. \_\_\_\_\_, Clark, C.E., Griffith, J.M., and Epstein, S.E. Mechanism of Left Ventricular Outflow Obstruction in Patients with Obstructive Asymmetric Septal Hypertrophy (Idiopathic Hypertrophic Subaortic Stenosis). Am. J. Cardiol. 35: 337-345, 1975.

Project No. Z01 RS 00009-05 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH

Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Nuclear Magnetic Resonance Techniques for Biochemical Analysis

Previous Serial Number: DRS-BEIB-6

Principal Investigators: Thomas R. Clem, Walter S. Friauf, Edwin D. Becker

Other Investigator: James A. Ferretti

Cooperating Units: LCP-NIAMDD, PSL-DCRT

Man Years:

Total:	2.0
Professional:	1.5
Other:	.5

Project Description:

Objectives: Innovate and implement improved methods for structural elucidation of organic molecules by means of nuclear magnetic resonance with emphasis on flexibility and convenience in selecting specific nuclei for study and the particular type of test performed.

Methods Employed: Develop and evaluate techniques for improving sensitivity and versatility, including use of a superconducting magnet, pulse train excitation with digital programming of the sequences, heteronuclear decoupling, real-time computerized data acquisition, digital averaging, phase correction, matched filtering, Fourier Transformation, and printout of spectra. Develop and evaluate Rapid Scan Fourier Transform NMR techniques as an intermediate alternative to CW and pulsed FT methods. Develop and evaluate improved methods of RF generation for greater reliability and flexibility.

Major Findings: NMR techniques can be used to routinely obtain parameters of organic molecules beyond those previously available including nuclei other than  $^1\text{H}$  and  $^{13}\text{C}$ .

Significance: Technique offers unprecedented capability for elucidation of organic molecule structure and, in particular, the location of  $^{13}\text{C}$ , et al, atoms. The high field strength of the superconducting magnet enables finer resolution than is obtainable with most other  $^{13}\text{C}$  NMR apparatus.



Proposed Course: Modifications with a second superconducting magnet to enable experiments with full-time application to  $^{13}\text{C}$  and related atoms.

Keyword Descriptors: Nuclear Magnetic Resonance, Fourier Transform NMR.

Honors and Awards: None

Publications:

Cohen, J.S., Bradley, R.B., Clem, T.R.: pH Dependence of the  $^{13}\text{C}$  Spin-Lattice Relaxation Rate of the Carboxyl Carbon of Acetic Acid. J. Am. Chem Soc. 97: 908-909, 1975.

Wasylishen, R.W., Clem, T.R., Becker, E.D. Nuclear Magnetic Resonance Chemical Shifts of Some Monosubstituted Isothiazoles. Can. J. Chem. 53: 596-603, 1975.

Project No. Z01 RS 00010-04 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Measurement of Low Level, Rapid Chemical Reaction Rates by Laser Jump, Temperature Jump, and Stopped Flow Techniques

Previous Serial Number: DRS-BEIB-9

Principal Investigators: Michael Greifner, P. Boon Chock

Other Investigators: None

Cooperating Units: LC-IR-NHLI

Man Years:

Total:	1.0
Professional:	.75
Other:	.25

Project Description:

Objectives: Measure incremental parameter changes corresponding to important biochemical reactions over a wide dynamic range. Develop a system capable of detecting and displaying chemical reaction rise times of less than 100 nanoseconds.

Methods Employed: Light absorption and fluorescence are monitored with photomultipliers. Dynode switching provides wide dynamic range without impairment of frequency response, linearity or accuracy. High intensity pulsed light sources improve the signal to noise ratio of nanosecond absorption measurements. Signal averaging techniques recover low level signals otherwise obliterated by noise. Improved data processing reduces investigator evaluation time for a typical experiment from weeks to days.

Major Findings: Development of new stopped flow cell reduces dead time from milliseconds to microseconds. Allows researchers to record reaction rates previously masked in mixing time of two chemicals. Stopped flowmeter with increased sensitivity provides an order of magnitude improvement in absorption level detection over commercially available instruments. High sensitivity is required to detect especially low level enzyme reactions.

Significance: Improved system sensitivity and frequency response enable new exploratory investigations into the complex mechanisms of various enzyme functions. State-of-the-art instrumentation for temperature jump apparatus and stopped flowmeters can provide information on the incremental, fast interactions between antibiotics with enzymes or proteins.

Proposed Course: Complete evaluation of stopped flowmeter reaction times. Patent new stopped flow cell. Design and develop multi-mix stopped flow apparatus. Design and develop pulse unit for high intensity lamps. Test and evaluate temperature jump apparatus. Design and develop instrumentation for detection of fluorescence and absorption time constants of laser temperature jump.

Keyword Descriptors: Laser temperature jump, stopped flow.

Honors and Awards: None

Publications: Rhee, S.G., Greifner, M.I., and Chock, P.B. ATP Determination by Stopped-Flow Method. Journal of Analytical Biochemistry (in press).

Project No. Z01 RS 00011-02 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Electrical and Electronic Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Electrical Safety Program for Clinical Center Patients and Patient Care Areas.

Previous Serial Number: None

Principal Investigator: Roland Corsey

Other Investigators: Corwin Strong, Anthony Vita, Walter S. Friauf

Cooperating Units: ADM-CC, SMS-BEIB

Man Years:

Total:	1.0
Professional:	1.0
Other:	0

Project Description:

Objectives: Establish a patient environment free of shock hazards and assure Clinical Center compliance with accreditation requirements regarding electrical safety.

Methods Employed: Establish NIH standards for the evaluation of commercial and non-commercial medical equipment; establish a testing program for all patient-contact electrical equipment; train nursing staff on the fundamentals of electricity and electrical safety; investigate and report on electrical accidents; conduct surveys of patient care areas to correct electrical hazards in grounding and power distribution; advise medical and nursing staff on new equipment purchases; participate in shaping of national, electrical safety standards.

Major Findings: The test program for medical equipment has uncovered instances of high electrical leakage current and poor grounding. Surveys of patient care areas have established the need for improved grounding and power distribution systems in critical care areas.

Significance: In critical care areas such as catheter laboratories, operating rooms and intensive care areas, the likelihood of accidental electricution has been reduced.

Proposed Course:

1. Train additional personnel on the fundamentals of electrical safety.
2. Extend the patient care area surveys to non-critical areas.
3. Extend the equipment testing program to test all new equipment before it is put into service.

Keyword Descriptors: Medical equipment, electrical safety standards, critical care areas.

Honors and Awards: None

Publications:

Friauf, W.S.: Test Equipment for Hospital Safety Programs. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 496.



Project No. Z01 RS 00012-04 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Atraumatic Electrical Sensing in the Human Brain Cortex

Previous Serial Number: DRS-BEIB-12

Principal Investigators: Seth Goldstein

Other Investigators: Edward M. Schmidt, John Van Buren, John Oakley

Cooperating Units: LNLC-NINCDS, SN-NINCDS

Man Years:

Total:	1.5
Professional:	1.0
Others:	.5

Project Description:

Objectives: (1) Achieve stable electrode location with respect to an active neuron for reliable actue extracellular recording of human brain cell activity within the pulsating cortex at prescribed depths up to 0.5 cm with minimum tissue damage.

(2) Extend this technique to achieve intracellular recording from the pulsating cortex.

Methods Employed: A microelectrode is supported by a gas bearing assembly and held within the cortex at the desired insertion angle. A fine lead screw is actuated by gas thrust bearings to retain the "floating" action during electrode depth adjustment. An electrocortigram is simultaneously obtained from the adjacent area of cortex.

Major Findings: The device has been successfully used to obtain high quality extracellular human recordings for prolonged durations. Intracellular recordings using glass micropipette electrodes have been obtained from pulsating monkey brain cortex.

Significance: Single-cell electrical recording from cerebral cortex in humans has been limited because of difficulty in atraumatically eliminating the effects of cortical motion. This new method is expected to markedly improve the acquisition of valid information necessary to enhance understanding of brain function and epilepsy.

Proposed Course: Extension of the technique to intracellular studies in human brain cortex; refinement of technique and apparatus, if necessary; clinical applications; extension of device family for related types of measurement requirements.

Keyword Descriptors: Single-cell electrical recording, extracellular electrical recording, intracellular electrical recording, neuroelectric recordings.

Honors and Awards: Goldstein, S.R.: Electrode Insertion Device for Neuroelectric Recordings. U.S. Patent No. 3,841,310 (October 15, 1974).

Publications:

Goldstein, S.R., Schmidt, E.M., Bierley, F.L., and Bak, M.: A Gas Bearing Mechanism for Atraumatic Electrical Recording from Individual Neurons in Human Cerebral Cortex. Transactions of the American Society of Mechanical Engineers, Journal of Dynamic Systems, Measurements and Control (in press).

Project No. Z01 RS 00013-01 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: In Vitro Muscle Studies/Hypertrophy

Previous Serial Number: None

Principal Investigators: Edward Lebowitz, Lawrence Thibault

Other Investigators: None

Cooperating Units: CB-NHLI

Man Years:

Total: 1.0  
Professional: 1.0  
Other:

Project Description:

Objectives: (1) To explicate the mechanism of cardiac hypertrophy in vitro using cat papillary muscle preparations.

(2) To investigate phosphorylation of papillary muscle in vitro (organ culture).

Methods Employed: Experimental apparatus has been developed in which cat papillary muscle is suspended in a constant temperature recirculating medium. PO<sub>2</sub> and PCO<sub>2</sub> of the medium are monitored as electrical stimuli are applied to the preparation.

Forces of contraction are measured concomitantly with gas tensions. Tissue growth is detected optically.

Major Findings: The preparations can be maintained viable for several days. This enables both phosphorylation and hypertrophy for adequate periods to reliably analyze both of these phenomena in vitro.

Significance: More detailed knowledge of hypertrophic mechanisms in cardiac muscle bears directly upon clinical diagnosis and therapy. Quantification of phosphorylation in cardiac muscle should contribute to the fundamental understanding of cardiac contractility.

Proposed Course: Improve and extend experimentation and analysis.

Keyword Descriptors: Hypertrophy, phosphorylation, organ culture,  
papillary muscle.

Honors and Awards: None

Publications: None

Project No. Z01 RS 00014-01 BEI

1. Biomedical Engineering and Instrumentation Branch
2. Mechanical Engineering Section
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

Project Title: Neural Trauma

Previous Serial Number: None

Principal Investigators: Lawrence Thiabult, Thomas Gennarelli

Other Investigators: None

Cooperating Units: Georgetown University

Man Years:

Total:	1.0
Professional:	1.0
Other:	.0

Project Description:

Objectives: To determine the effects of mechanical strain on nerve tissue function. To investigate the role of mechanical strain on nerve tissue membrane transport regulations.

Methods Employed: Equipment has been developed which permits controlled loads to be applied to isolated neural tissue. Mechanical stress and strain are measured concomitantly with electrophysiological parameters and associated biochemical changes.

Major Findings: Mechanical strain affects neural function. Compound action potentials are modulated by strain, both fully reversibly and irreversibly depending upon the level of strain. Biochemical changes, e.g. potassium movement, occur simultaneously, suggesting membrane permeability changes.

Significance: Elucidation of the effects of membrane strain on chemical transport processes contributes substantially to the basic understanding of fundamental physiological mechanisms.

Proposed Course: Refine and extend experimental and analytical techniques for nerve cells and other tissues.

Keyword Descriptors: Nerve tissue, neural trauma, membrane transport, mechanical strains.



Honors and Awards: None

Publications:

Gennarelli, T.A. and Thibault, L.E.: Functional response of the central nervous system to controlled inertial loading. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 175.

Thibault, L.E., Gennarelli, T.A., Tipton, H.W. and Carpenter, D.O.: The physiologic response of isolated nerve tissue to dynamic mechanical loads. In Proceedings of the 27th Annual Conference on Engineering in Medicine and Biology, 1974, Philadelphia, Pennsylvania. Arlington, Va., The Alliance for Engineering in Medicine and Biology, 1974, Vol. 16, p. 176.

DIVISION OF RESEARCH SERVICES

Summary of Program Activities

July 1, 1974 through June 30, 1975

ENVIRONMENTAL HEALTH AND SAFETY PROGRAM

Dr. Rudolf G. Wanner  
Associate Director

I. SUMMARY

1. Office of the Associate Director for Environmental Health and Safety

The transfer of the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, to the Division of Research Services as the Radiation Safety Program, took place on July 1, 1974. On the same date, the Safety Management Program transferred to DRS. On December 23, 1974, the Associate Director was appointed and given responsibility for the development of a well-integrated, comprehensive and centralized environmental health and safety program. Further progress toward centralization of functions was made on March 1, 1975, when the responsibilities for implementation of the National Environmental Policy Act (NEPA) were assigned to the Associate Director.

2. Environmental Services Branch

Two major program events caused a complete reorientation of activities in the Office of the Chief which, in turn, added to the workload of the Branch's two Sections. The first event was the organization of the Environmental Health and Safety Program within DRS.

The second event was the sudden increase of activities generated by the National Environmental Policy Act which escalated beyond predicted levels. Sixteen EPA effluent guidelines and several non-DHEW environmental impact statements were reviewed for the Office of the Assistant Secretary for Health, DHEW. Staff assistance was provided to the Division of Engineering Services in preparing the environmental assessment of the NIH Master Plan involving approximately sixteen construction projects.

Staff assistance was provided to the Assistant Director for Administration, NIH, in the Generic Analysis of all NIH programs. Staff also served on a task force of the Assistant Secretary for Health, DHEW, to develop proposed Departmental regulations and procedures for implementation of NEPA.

The national concern for employee health and safety was reflected in the ESB workload. Thirty-two employee requests were investigated concerning suspected hazards in their work places and three extensive surveys were conducted for requested Environmental Differential Pay. Three formal OSHA complaints were also reviewed and 108 other laboratory surveillance visits directly related to employee health were made.

The Branch concern for environmentally safe and sound facilities and equip-

ment continued. The major equipment problem remains procurement of Laminar Flow Biological Safety Cabinets. Two pathways were simultaneously pursued; one the continued development of a Qualified Products List and the other a proposal to the National Sanitation Foundation to develop a joint industry and public health supported standard and certification procedure. The Branch expended 80 mandays in the field performing acceptance tests in order to "speed up" the process. Staff worked cooperatively with individual investigators and other DRS staff in designing new or modified equipment in 24 instances. In addition, 66 Laminar Flow Biological Safety Cabinets were modified by an ESB contractor, and 118 chemical fume hoods are being up-graded cooperatively with the Division of Engineering Services. Fourteen major construction projects were reviewed continually to assure proper environmental safeguards.

Investigator requested consultation on procedures, equipment and basic information remains high. Approximately one manyear was spent in providing this information on a person-to-person basis. Eighty percent of the requests are from the intramural programs. In addition to the person-to-person consultations, mail requests for environmental health and safety information are mounting. This is reflected in the 300 plus mailings of the "Biological Laboratory Hazards" memorandum and provision of over 400 copies of the Biohazards Safety Guide to non-NIH investigators.

### 3. Radiation Safety Program

On July 1, 1974, the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, was transferred to DRS and designated the Radiation Safety Program. As a part of the consolidated environmental health and safety program and in an effort to improve current operations, an Acting Deputy Head of the Radiation Safety Program was appointed.

Major program efforts consisted of assurance of compliance with the regulations of the Nuclear Regulatory Commission, formerly the Atomic Energy Commission. The NRC issued seven licenses to NIH for the use of radionuclides. Possession of these licenses has greatly reduced the detailed problems of isotope procurement, but carries strict responsibilities governing use and ultimate disposal.

License renewals and amendments were obtained to permit the installation of two irradiators at the Clinical Center, one of 2400 curie capacity, the other of 500 curie. Physical and radiation problems encountered during and after the initial installation were satisfactorily solved.

The use of radionuclides for diagnostic, therapeutic, and research purposes is rapidly increasing at NIH. Although users of radioactive material are required, as part of the NRC regulations, to show proof of training in the safe handling of such substances, radiation incidents continue to occur. These incidents were in their majority due to human errors, thus preventable. Whenever physical factors were the cause, the Radiation Safety Program took prompt remedial action.

All authorized users of radioactive iodine were notified of an additional safety requirement. As of October 1974, no iodinations are permitted in hoods without charcoal filters. This requirement was met by being able to accommodate investigators in doing their iodinations in Building 21, which has a sufficient number of hoods with charcoal filters.

Under NRC requirements, the Radiation Safety Program is responsible for receiving, shipping and disposal of radioactive materials. An increase of 17% in the number of shipments received reflects the increased use by NIH investigators. To this workload were further added new regulations for receiving and opening packages, checking for contamination at the time of arrival. Consequently, manpower had to be provided on weekends and holidays.

Radioactive waste volume increased by 31% for the reporting period. Improvements in the waste handling area consisted of equipping the waste compactor with a HEPA filter to prevent radioactive aerosols from escaping into the work environment, and of installing a ventilated hood for the storage of volatile radioactive wastes.

Laboratory surveillance was maintained at a high level and carried out in the nearly 1500 areas where radioactive materials are being used. Strong emphasis was placed on the control of airborne radioactive substances. The number of air samples taken increased by 271% over the previous fiscal year. Investigation and remedial action took place where contamination was found.

Surveys of diagnostic, therapeutic and research x-ray units were made routinely and by request. In only one instance, a significant radiation hazard was found, an x-ray diffraction unit had to be shut until corrective action was taken. Shielding and other protective recommendations were made for other units where a hazard potential existed. In addition, 50 electron microscopes were surveyed for x-ray leakage.

Personnel monitoring for exposure continued as a routine activity. The number of users of film badges, or external radiation personnel dosimeters increased by 9% over the last fiscal year. An important improvement was the replacement of ring badges by thermoluminescent dosimeters.

The new dosimeters do not have to be worn on the hand, which makes them more acceptable to the user and less prone to water damage.

Investigators and workers working with certain levels of radioactive materials and specified substances are required to submit urine specimens for radioassay. The number of specimens assayed increased by 6% during the reporting period. The number of whole body counts, required by NRC of users of gamma emitting radionuclides, increased by 17%.

The Radiation Safety Program continued to provide training in the safe handling of radioactive materials. Over 850 individuals attended training courses, most of them the one-day course entitled, "Radiation Safety in the Laboratory."

#### 4. Safety Management Program

Accident reports processing has been improved substantially by using a computer-based system. This system allows for a better data analysis and makes it possible to identify more precisely areas and activities with high accident rates. Consequently, preventive and corrective measures can be more accurately applied.

Accident investigations were conducted on a continuing basis by safety specialists. The NIH accident and injury reporting system continued during the reporting period to function on a recognized better level than most DHEW agencies. The close coordination of this activity with the Employee Health Service and other branches kept reporting close to 100%. Wherever necessary, remedial action was taken and recommendations were given. Fire prevention continued to be of major concern. A report, "NIH Fire Safety Posture", was completed. In it, each building on the NIH Bethesda location is described and discussed with regard to fire safety. The report provides a basis for eliminating fire hazards and for up-grading NIH facilities to prevent losses from fire.

In other accident prevention activities, efforts continued to survey the NIH work environment for compliance with Safety Standards and to examine potential accident producing situations. A concentrated effort was made to clear the corridors and elevator lobbies of the Clinical Center from excess storage of items. The photographic survey made to document unsafe conditions was made available to those responsible for and using the areas in question. Subsequent surveys showed some improvement, but not to the extent desired.

Following a request from the Division of Engineering Services, an "Industrial Safety Guide" was under development through the reporting period. It is one of a series of guide books issued by the Safety Management Program. The "Supervisor's Guide to OSHA" was prepared and distributed as a publication which identifies workplace safety standards set by the Occupational Safety and Health Act as they are applicable to the NIH environment. A "Safety Guide for Contract and Project Officers" is being reviewed and should be available by mid-FY 76. It will enable the Division of Contracts and Grants, OD, to include an up-to-date safety and health clause on contracts where applicable and required.

There was a wide range of training activities throughout the year. An important part is the new employee orientation for Clinical Center and ADA personnel. Safety specialists contributed with presentations and material to a variety of NIH training courses. In addition, three slide/cassette programs on Research Laboratory Safety, Safe Driving and Workmen's Compensation were completed. A new training course on Biohazards Safety is under development. This course may become a requirement for laboratory workers handling hazardous biological agents.



## II. PROGRAMS

### A. Objectives

To function as the central manager, coordinator and regulative authority over the Environmental Services Branch, the Radiation Safety Program and the Safety Management Program in support of the Director, DRS, to achieve Division objectives pertaining to environmental health and safety.

To administer a comprehensive environmental health and safety program for NIH.

To establish, interpret and monitor compliance with policies and standards which serve to maintain and protect health, safe working conditions and environmental quality for the NIH community.

To provide related technical, surveillance and training services.

### B. Current Programs

The Associate Director supervises and coordinates the current programs of the component units. These include:

1. The establishment of standards, policies and guidelines for environmental health and safety, and their application.
2. Analysis of data and interpretation of regulations to develop solutions for the elimination of environmental, radiation and other safety hazards.
3. Implementation of the requirements of federal, departmental and agency regulations at NIH.
4. Laboratory support services for the NIH environmental health and safety program.
5. Training services as required by federal regulations.
6. Training development as specific needs at NIH are recognized and identified.
7. Surveillance for environmental, radiation and other safety hazards by a monitoring system.
8. Maintenance of registries of biological agents, radioactive materials, chemical carcinogens and other substances of known or suspected hazardous potential.
9. Review of Technical Reports on environmental health and safety from or for NIH, PHS, DHEW and other sources.

10. Maintenance of a reporting and information system on environmental health and safety at NIH.

C. Program Progress and Accomplishments

1. Office of the Associate Director for Environmental Health and Safety

The transfer of the Radiation Safety Section, Department of Nuclear Medicine, Clinical Center, to the Division of Research Services as the Radiation Safety Program, took place on July 1, 1975. On the same date, the Safety Management Program transferred to DRS. These were major steps of progress towards a consolidation of NIH environmental protection programs, with the Environmental Services Branch already in the Division.

On December 23, 1974, the Associate Director was appointed and given responsibility for the development of a well-integrated, comprehensive and centralized environmental health and safety program. Consequently, a considerable amount of time and effort was spent in the second half of FY 75 on the identification of existing problems and their solution within the newly established program. At the same time, continuity of services by the component units was maintained.

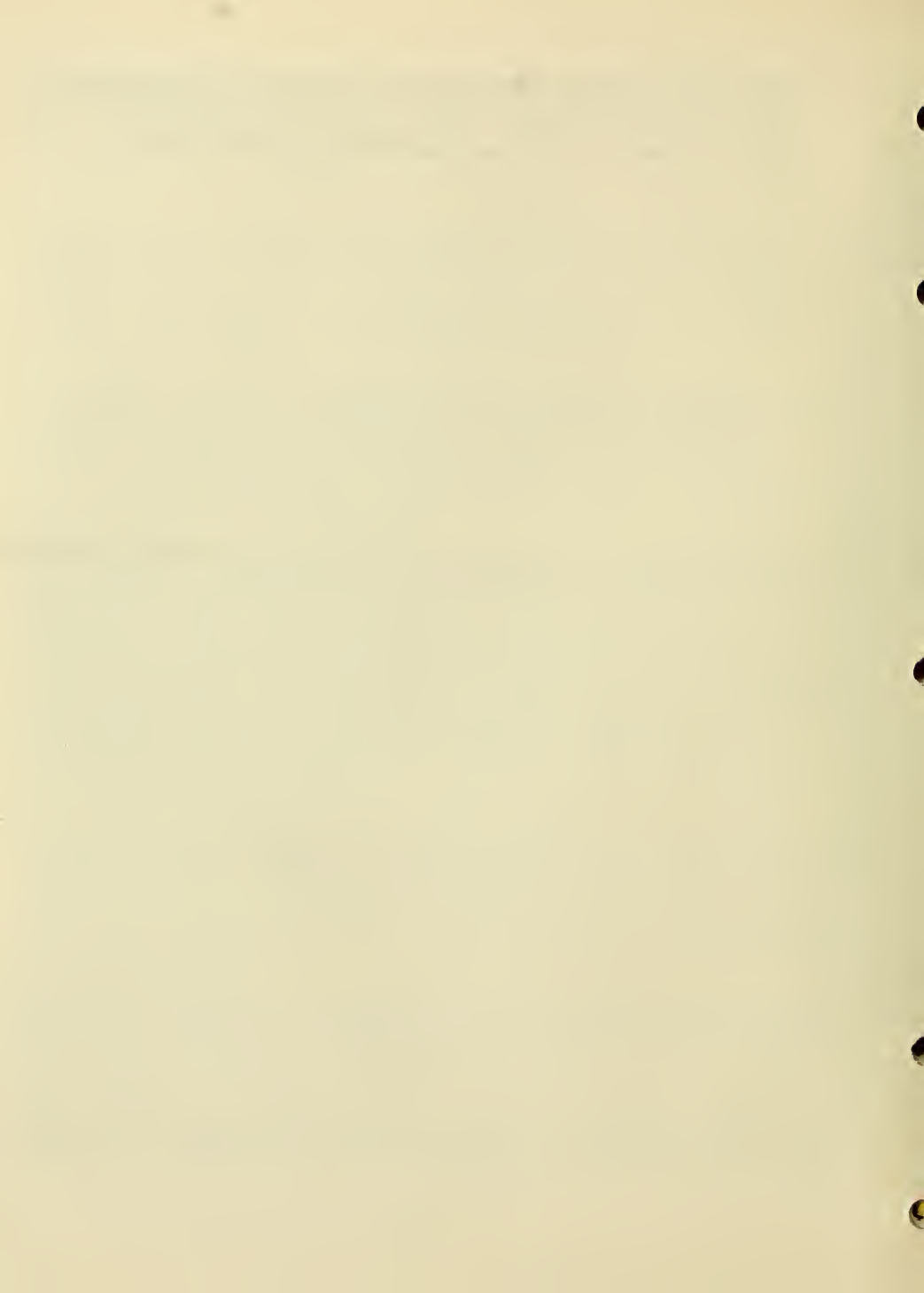
Further progress toward centralization of functions was made on March 1, 1975, when the responsibilities for implementation of the National Environmental Policy Act (NEPA) were assigned to the Associate Director. As Agency Environmental Officer, he is responsible for assuring NIH compliance with the Act. This includes preparing NIH policy and procedures, the receipt and processing of all technical review requests, and NEPA training activities. The transfer of NEPA responsibilities was another major step towards achievement of FY 75 objectives. It made it possible to coordinate and administer a comprehensive program, since the responsibilities for implementation of the other major requirements, the Occupational Safety and Health Act (OSHA) and the Nuclear Regulatory Commission (NRC), were already inherent in the program.

The Associate Director and selected staff are members of NIH committees relating to environmental health and safety, such as the Biohazards Committee, Radiation Committee, Infections Control Committee and their various sub-committees to provide technical advice to NIH research and service functions, to identify problem areas, to make recommendations of their solution and to review and recommend procedures and technical information for risk assessment and reduction of hazards.

A close working relationship was established with the Office of Research Safety, NCI, resulting in coordination of activities, such as the maintenance of a chemical carcinogen registry, inspection of biological safety cabinets and evaluation of laboratory containment facilities.

Past experience and repeated incidents of the same nature have demonstrated that the NIH research population is not always aware of special investigations carried out, remedial action taken and preventive recommendations made. The issuance and distribution of Environmental Health and Safety Special Invest-

igations Reports (EHSSI) was introduced. These reports will be prepared whenever a particular incident study of interest to the scientific community has been completed. The Environmental Health and Safety Program, through its component units, as a whole accomplished its objectives for FY 75.



## BRANCH PROGRAMS

A Objectives

The Environmental Services Branch objectives at NIH, Bethesda, Maryland, and field station facilities are:

1. To locate and solve environmental problems.
2. To assure a safe, compatible environment for patients, staff, and the surrounding community.
3. To promote an environment conducive to a quality research program.

B. Current Programs

The Branch objectives were attained through the following closely coordinated program areas:

## 1. Biohazards and Contamination Control

The biohazards and contamination control program is designed to promote a safe environment for personnel and to protect research work at all NIH facilities in Bethesda and in the field. There is a regular surveillance of potentially hazardous laboratory and animal room areas, control equipment and facilities. Consultation is provided on a case-by-case basis for laboratory arrangements needed to protect the investigator and the public.

## 2. Industrial Hygiene

The industrial hygiene program recognizes, evaluates, and controls environmental factors and stresses which may cause illness or significant discomfort among workers or citizens of the community. Gaseous and particulate air contamination potentially or actually generated at NIH and laboratory use of chemical carcinogens are major surveillance activities. Problems of noise, temperature extremes, and non-ionizing radiation are also investigated and resolved.

## 3. Hospital Environmental Control

The hospital environmental control program in the Clinical Center is designed to protect patients, employees, and visitors from environmental influences which may be unsafe, unhealthful, or uncomfortable.

#### 4. General Sanitation and Sanitary Engineering

The general sanitation and sanitary engineering program is concerned with basic environmental factors affecting the health of NIH employees, visitors and the quality of the research environment. These factors include food sanitation, water supply, solid and liquid waste disposal, housekeeping practices, pesticides, and water pollution control.

#### 5. Environmental Studies for Support of Research and Patient Care

Continuing environmental studies are conducted as a necessary adjunct to surveillance and consultation activities. Studies are oriented to environmental systems and problems; evaluation of new equipment and methods; quality glassware, animals, and water; environmental stresses related to light, heat, noise, food, water, and waste; and the identification of environmental contaminants.

#### 6. Training

Training to promote job effectiveness is provided for ESB personnel and staff members at NIH. This training is particularly related to environmental control devices and practices in the general research environment which require special training for proper operation and handling.

### C. Program Progress and Accomplishments

#### 1. Biological Control

The NIH Biohazards Safety Guide was developed and printed in two formats. A looseleaf edition permitting continuous updating as new biological safety developments occur has been distributed to NIH laboratory investigators. A perfect bind edition is available for investigators outside NIH, either as single copies furnished upon written request or in quantity from the Government Printing Office, Superintendent of Documents. The Guide will be published in Spanish by the Pan American Health Organization, Washington, D. C.

A new questionnaire for registration of microbial agents, tissue cultures and animals was developed and distributed to laboratory workers. Included in the questionnaire were requests for information on serum samples, their storage, concentration of agents, and volumes of fluids handled. The information obtained has been placed in a computer data bank. Readouts on microfiche cards are broken down into several categories; lists of individuals by name alphabetically and by social security number, listing by building and room number and listing of employees by item (microbial agent, tissue culture or animal).

A chamber for the decontamination of equipment has been constructed in Building 13. It will serve to sterilize equipment shipped to Surplus Property, Materiel Management, ODA; to instrument repair in the Biomedical Engineering and Instrumentation Branch, DRS; or to companies outside NIH, as necessary, to reduce any biohazards.



ESB assisted the Procurement Branch, Materiel Management, in making seven site visits to manufacturers of Class II Laminar Flow Biological Safety Cabinets for field testing and evaluation of cabinets for compliance with the NIH Specification. Test data and drawings were reviewed by staff personnel before each visit. Approximately eighty mandays were involved.

ESB initiated a request to the National Sanitation Foundation, Ann Arbor, Michigan, to develop performance standards for the Class II Laminar Flow Biological Safety Cabinet. As a result, members of the Biological Control Section are serving on a committee to develop the standards. Under this standard, the NSF would be responsible for carrying out necessary tests, publishing a list of approved models by manufacturer and controlling the quality of the equipment. Such a standard would reduce the commitment of ESB to Materiel Management, ODA, and shorten the delivery time of the cabinets.

Fourteen plan reviews of major building renovations at different stages of design were made. These included the renovation of Building 376, Fort Detrick, Maryland, to house the NINCDS slow virus program; the open bay area in Building 41; and Building 14D to house infected primates. Approximately fifteen draft reviews of such items as the Clinical Center Biological Disaster Plan, the National Sanitation Foundation's Standard for Biohazard Cabinetry and the Design Criteria for Viral Oncology Research Facilities were performed. Programs of Requirements for a large number of laboratories in Buildings 36 and 41 were also reviewed.

The number and subject of consultations with individuals at NIH and outside NIH are shown in the following table (each consultation averaged four hours:

	<u>NIH</u>	<u>Outside</u> <u>NIH</u>
(a) Selection of Equipment	70	14
(b) Proper Use of Equipment	11	1
(c) Safety Devices and Biohazards Control	81	38

Modification of equipment included the development of a safety cabinet for handling biological agents and radionuclides; the modification of a Laminar Flow Biological Safety Cabinet to permit the handling of nude mice under sterile conditions; and in conjunction with the Biomedical Engineering and Instrumentation Branch, DRS, development of a ventilated containment hood for a freeze fractionator unit that will be used for work with scrapie virus.

Investigations were made in response to employee requests for evaluation of their work environment for hazardous conditions. These included microbiological assessment of air quality at the incinerator; review of laboratory procedures related to a possible laboratory-acquired serum hepatitis case; microbiological aerosol of NIHAC Waste Treatment Plant; and the NIHAC Primate Quarantine Facility.

An ESB contractor conducted a survey to analyze facility and systems adequacy of selected biological laboratories performing hazardous work.

Sixty-six Laminar Flow Biological Safety Cabinets were modified under contract to provide more air velocity in-flow at the work access opening, thus providing greater protection to the investigator.

A "re-certification" of the containment capabilities of the secondary barrier systems in the Building 36 Virology Suite was completed.

Seven thousand six hundred and thirty-eight (7,638) bacteriological tests were performed in the analysis of patient food and milk, potable water and waste water, and other environmental samples.

## 2. Industrial Hygiene

The Occupational Safety and Health Act of 1970 and subsequent Presidential Directives and Regulations published in the Federal Register generated a major workload for the industrial hygiene program. In one instance, a complaint was filed with OSHA via the Congress which required a special survey of working conditions in the NIH Power Plant.

Compliance with OSHA Regulations for control of chemical carcinogens in the NIH research environment continued to provide a major workload. A special in-depth survey of select animal rooms, laboratories, and other spaces reporting the use of chemical carcinogens was completed by an ESB contractor. This survey indicated that facilities and work practices require improvement to assure a safe and healthful work environment.

ESB reviewed and commented on proposed DHEW regulations to control chemical carcinogens in the research environment. This issuance should clarify the responsibilities of management, the worker, and safety personnel.

An ESB contractor completely surveyed and labeled 761 NIH chemical fume hoods. A large number of hoods (118) did not meet minimum standards. A cooperative project with the Division of Engineering Services to upgrade these hoods is being undertaken.

An independent evaluation was made of the recently designed NCI Laminar Flow Biological Safety Cabinet under contract to determine if its performance as a chemical fume hood is acceptable. Several potential problems and limitations on its usage were identified.

ESB, in cooperation with BEIB and the Radiation Safety Program, developed and tested a small hood for use within a standard chemical fume hood to remove gaseous radioactive iodine from the air before it is discharged to outside air via the existing exhaust system. The hood has a top mounted charcoal filter and blower. Its use should greatly reduce the number of reportable radioisotope release episodes.

Increasing concern about noise, both as a health hazard and as an interference in the work environment, resulted in a continued large workload in making the various evaluations and determining the required corrective measures.

An improved system for disposal of chemical waste at NIH was implemented this year. The NIH Fire Department carefully packages waste chemicals for disposal or recycling by a contractor. Remaining acids, bases, and a few special chemicals not disposed of by this means are disposed of at NIH in its special facility. Plans for upgrading the chemical packaging and disposal facility have been completed.

### 3. Hospital Environmental Control

This program continued on a low priority basis due to reduced staffing. A member of the Biological Control Section was assigned on a part-time basis to provide requested surveillance and monitoring services. The Operating Room Surveillance Protocol was reestablished in cooperation with the Surgical Nursing Service and the Infections Control Committee.

### 4. General Sanitation and Sanitary Engineering

Semiannual surveys were made of all GSI Cafeterias and Blind Industries and Services of Maryland snack bar facilities, both on and off the main NIH reservation. Brief visits were regularly made between surveys to assure continued high quality food service sanitation.

Continued monitoring of general NIH outside "grounds" sanitation, including loading docks, showed some improvement this year.

A new NCI animal care program is expected to improve animal room sanitation in the coming year.

Routine analyses of NIH and NIHAC central distilled water systems for specific resistance, and potable water systems for chlorine content and microbial quality were continued. In addition, copper analyses of the various distilled water systems were made quarterly and special analyses for selected high purity systems were provided as needed.

The Branch completed sixteen EPA Environmental Impact document reviews in support of the NIH Agency Environmental Officer.

Solid waste at NIH presented a major workload ranging from individual sanitation problems of improper waste disposal to reviews of building system plans. A major effort was mounted in terms of trials of paper bag and paper board box systems which will replace "G.I." cans when the Montgomery County Pathological Incinerator and the new NIH Back-up Pathological Incinerator are put into use in FY 76 and FY 77.

Monthly visits were made to the NIHAC to conduct sampling at the Sewage Treatment Plant, Broad Run and Lagoon #2. At the same time, waste water samples were also taken from the NIH storm drains and analyzed. Samples

were taken from NIH sewers for mercury analyses. The Branch was involved with the EPA in a special study of waste water effluent from the Clinical Center. Assistance was provided DES in selection of an engineering consultant who will develop plans to upgrade the NIHAC Waste Water Treatment Plant.

Air quality data from the Maryland monitoring trailer located on the NIH grounds was obtained from computer tapes supplied by the state and a program prepared to extract and report the pertinent NIH data.

## 5. Environmental Studies

An extended study of mold spores in the Clinical Center was initiated in collaboration with the Clinical Mycology Section, Laboratory of Clinical Investigation, NIAID. Of special concern is the relationship of aspergillus found in the air supply and aspergillus infections which have been seen in increasing numbers of immunosuppressed patients.

A study was completed of the biota of Broad Run at the NIHAC. The study involved an extended survey of "bottom life" of the stream above and below the Waste Treatment Plant. ESB staff was assisted by a professional marine biologist under contract with ESB.

An improved all-glass water still was developed to meet the high purity water demands of several investigators. The still has the unique capability of maintaining long "shelf life" sterility of the distilled water.

A study of the sterility, shelf life and various methods for packaging and sterilizing materials used in nursing units was conducted for the Pharmacy Department, Clinical Center.

## 6. Training

ESB continued participation with other NIH safety groups in developing laboratory safety posters which are displayed throughout the campus and are printed in the NIH Record. This is an effort to raise the safety awareness level of NIH employees.

The Quarterly Memorandum, "Biological Laboratory Hazards," is apparently meeting a need at NIH and in collaborative laboratories. The mailing list now exceeds 300 laboratories, including several overseas institutions. The Laboratory Infection Bibliography, developed under contract, will supplement the memorandum.

Nine presentations were made to separate intramural laboratories on proper laboratory practice. In addition, staff attended five Institute Laboratory Chiefs' Meetings to discuss the "Biohazard Safety Manual" and related matters. The sixteen-hour laboratory practice course was again presented to summer student employees. Four hundred NIH employees attended a series of training sessions on noise hazards and hearing conservation presented by the Branch.



Demand for Branch personnel as lecturers and speakers in all facets of environmental health and safety remained high. Of particular interest was participation in hearing conservation programs presented to two sixth grade Elementary School classes. Technical presentations were given to the Metropolitan Area Construction Safety Association, The American Industrial Hygiene Association, National College Health Association, 17th Annual Biological Safety Conference, Michigan Environmental Health Association, National Metropolitan Area Environmental Health Association, American Association of Laboratory Animal Sciences, Kentucky Hospital Association, American Society for Microbiology and the Tissue Culture Association. Staff also lectured at the NIOSH course, "Safety In The Laboratory."

ESB personnel received 913 hours of training at designated short courses or in classroom experience at colleges and universities. Two COSTEP trainees received on-the-job experience in the Branch.

#### D. Problems

The unplanned changing scope and direction of ESB's program is creating an adverse impact on allocation of resources. New laws and directives concerning the environment unpredictably superimpose a workload on ESB's basic service effort. Special studies and document reviews for OSHA and NEPA have deadlines precluding work planning that ensures NIH investigators receive the personal services that ESB is supposed to provide. Contracting with private firms has helped remove some of the routine workload; however, contracts require ESB staff time for preparation, to monitor the contractor, to evaluate the results of the contractor's efforts and to see that NIH acts on contractor recommendations. Hopefully, program plans of the NIH Environmental Health and Safety Program will solve this problem.

The procurement of Class II Laminar Flow Biological Safety Cabinets to meet the needs of NIH scientists is continually faced with long delivery schedules of one year or more. This hampers planning for biological research that require this equipment. In an effort to improve delivery schedules, ESB has provided review of test data, drawings and made site visits to manufacturers of this equipment to help eliminate problems with compliance to the NIH specification. Technical advice is being provided to the National Sanitation Foundation in their development of a performance standard for the manufacture of this equipment.

#### E. Program Plans

The Branch programs will be integrated into the overall scheme of the DRS Environmental Health and Safety Programs. A realignment of ESB staff into functional work units based on program demands and objectives in keeping with professional backgrounds is planned. A major decision must be made concerning manpower utilization considering the following factors: Technical assistance demands from NIH intramural and extramural investigators and programs, necessary surveillance and outside legal directives concerning environmental health and safety. Assistance is anticipated in training activities with consolidation of this activity into the Associate Director's office. Decisions regarding programming will be developed

jointly with the other DRS Environmental Health and Safety components to present a balanced program.

Contracting for services in FY 75 will continue at approximately the same level as in FY 74. It is expected that some analytical work will have to be contracted out for those materials of environmental concern that we cannot analyze in our own laboratory.

F. Publications and Patents

Herman, L.G.: Disinfectants and Environmental Monitoring. In Proceedings of a Seminar Presented at the 23rd Annual Session of the American Association for Laboratory Animal Science, Joliet, Illinois, Pub. 74-5, pp. 38-44, 1974.

Herman, L.G.: Environmental Microbiology and Infection Control Programs in Health Care Facilities: Introductory Remarks. Helath Laboratory Science 11: No. 2:6970, 1974.

Waters, P.F., Hadermann, A.F., and Karamian, N.A.: Aseptic Aerosols From Cold Vapour Humidifiers. Lancet 739-740, 1974.

Herman, L.G.: The Hospital Environment. Professional Sanitation Management. Issue 6:11-14, Issue 7:20-23, 1974.

Irwin, J.: A Trap and Filtration Apparatus for Vacuum Lines. Health Laboratory Science 11: no. 3:195-196, 1974.

Wilkinson, T.K: Ultraviolet Radiation as a Disinfectant. In Proceedings of a Seminar Presented at the 23rd Annual Session of the American Association for Laboratory Animal Science, Joliet, Illinois, 1974.

McCoy, Z. and Irwin, J.: The Effect of Disinfectants on Bacteriophage ØX 174 1,2. Lab. Anim. Sci. 24:no. 4:630-632, 1974.

DeRoos, R.L., Oviatt, V.R., DuChene, A.G. and Vick, N.J.: Water Use in Biomedical Research and Health Care Facilities--A Presentation of Article Summaries. Div. of Env. Health, School of Public Health, Univ. of Minn., Minn., Minn., pp. 163, 1974.

Farmer, J.J., III, Herman, L.G.: Pyocin Typing of Pseudomonas aeruginosa. J. Infect. Dis. Vol. 130, Supplement: S43-46, 1974.

Voxakis, A.C., Lamy, P.P., Herman, L.G.: Sterility Assurance Through Environmental Monitoring. Hosp. Form. Mgt. pp. 14-19, 1974.

Dunsmore, D.J.: Wylbur "Talks" to DRS. INTERFACE pp. 17-19, No. 53, December 25, 1974.

Karamian, N.A.: Separatory Funnel, U.S. Patent #3,836,334, Issued September 17, 1974.



## BRANCH PROGRAMS

A. Objectives

The objective of the Radiation Safety Program is to assure compliance with Part 10, Code of Federal Regulations, Chapters 19 and 20, conditions of licenses granted by the Nuclear Regulatory Commission (NRC), other applicable Federal regulations, and all policies established by DHEW and NIH in regard to the safe use of ionizing radiation so as to assist the NIH researcher in obtaining the maximum benefit from ionizing radiation while maintaining personnel exposure and the release of radioactive materials to unrestricted areas at the lowest practicable levels.

B. Current Programs

The program objectives were achieved through the following closely coordinated program areas.

## 1. License Activities

License activities include a continual review of the seven licenses issued to NIH by the Nuclear Regulatory Commission which permit the receipt, storage, use and disposal of radioactive materials in accordance with Nuclear Regulatory Commission regulations and standards. License applications, renewals, or amendments are prepared and submitted to NRC as necessary. A semiannual inventory of all radioactive materials is conducted to ensure that possession limits prescribed by the NRC are not being approached. New or proposed legislation or regulatory guidelines are thoroughly reviewed for impact on the Program. The administrative aspects of license activities are conducted in close coordination with the Radiation Committee and NIH Management.

## 2. Radionuclide Shipping and Receiving

The radionuclide shipping and receiving program covers all radioactive materials coming to or leaving the NIH reservation. All incoming shipments are checked for contamination, proper labeling and packaging, damage, and correct compound, isotope and activity. A check is made as to whether the individual ordering the material is authorized by the Radiation Committee to work with radioactive materials.

## 3. Radioactive Waste Disposal

The radioactive waste disposal program includes supervision and coordination

of the waste disposal program, including the waste disposal records. These activities are conducted under the conditions of License No. 19-00296-11, issued by the NRC.

#### 4. Patient Therapies and Diagnostic Studies

Health physics support is provided to patients receiving therapeutic doses of radioactive materials and in some diagnostic studies to ensure that: they receive the dose prescribed, personnel exposures are as far below permissible levels as practical, and there is compliance with all applicable regulations and policies.

#### 5. Radiation Safety Surveillance

The surveillance program consists of routine surveys in all laboratories where radioactive materials or other equipment capable of producing ionizing radiation are used. The areas are checked for compliance with the provisions of 10 CFR 19, 10 CFR 20, Occupational Safety and Health Act, and other policies and standards approved or promulgated by the Radiation Committee. Appropriate followups are made to secure compliance and in the case of repeated or highly hazardous conditions, the matter is referred to the Radiation Committee for appropriate corrective action.

#### 6. Personnel Monitoring

The personnel monitoring program monitors radiation workers to determine radiation dose from external sources and internally deposited materials. This generally consists of film and thermoluminescent dosimetry, whole body counts and radioassays of urine samples. It involves record keeping of lifetime exposure histories, review and distribution of the results, and if necessary, appropriate remedial action.

#### 7. Training

The training program goal and activities are aimed at making all radiation workers fully aware of the regulations and policies governing the safe use of ionizing radiation, to be cognizant of the hazards associated with its use, and to inform and motivate radiation workers with regard to use procedures and equipment which will minimize personnel exposures. The provision of such training is mandatory under the requirements of 10 CFR 19 and the Occupational Safety and Health Act.

#### 8. Technical Assistance and Other Radiation Safety Services

The technical assistance program includes consulting services to personnel at all levels on all aspects of radiation protection. Space is available in Building 21 for handling high levels of activity. Shielding materials are provided, and portable survey meters are issued to laboratories. The survey meters are calibrated semiannually and repaired as needed. In addition, technical assistance is given to the researcher to effectively use ionizing radiation in the conduct of biomedical research. Supervision and assistance is also provided in contaminating accidents. Increasingly,

requests for technical assistance are received from NIH field stations, other components of DHEW, other federal agencies, state and local governments, universities, business organizations and concerned citizens regarding radiation safety.

C. Program Progress and Accomplishments

1. License Administration

License No. 19-00296-17 was amended to permit the installation of a 2,400 Curie Cs-137 irradiator in Building 10 for irradiating mice and conducting other in vitro studies. The unit is similar in size and design to the existing blood product irradiator in Building 10, Rm. 3B11. A survey was conducted at the time of installation. There was a question regarding structural stability of the legs. This was corrected and the matter was referred to the NRC for further investigation.

License No. 19-00296-12 was renewed and was also amended to permit relocation of the 500 Curie Co-60 irradiator from Building 10, Rm. B1-B52 to Room B2-B52, and after renovation it will be permanently installed in Room B2-B54. A radiation survey conducted after the initial move, required by a license condition, indicated radiation leakage. Additional shielding satisfactorily corrected the problem.

License No. SUB-985, which permits use of depleted uranium as beam defining devices in two linear accelerators, was renewed by the NRC.

On November 21-22, 1974, an NRC representative Division of Regulatory Operations, Region I, conducted an inspection of License No. 19-00296-10. The results indicated satisfactory progress in the areas of personnel training and the control of releases of radioiodine to the lowest practicable level. Occasional failure of investigators to collect breathing zone air samples during iodinations was noted. A reply was prepared outlining the administrative controls established to assure compliance with this requirement. Copies of the inspection report and the NIH reply were posted on bulletin boards in all buildings where radioactive materials are used as required by 10 CFR 19.

Semiannual accountability reports for the special nuclear material contained in the plutonium-powered pacemakers (License No. SNM-279) were submitted on a timely basis to the NRC.

Approximately 200 sealed sources were checked for leakage on a semiannual basis as required by License No. 19-00296-10.

There were several radiation incidents requiring NRC notification. The most significant were a 600 rem body badge exposure to a physician with the Metabolism Branch, NCI. The individual definitely did not receive this high a dose, however, no plausible explanation of this exposure could be determined. Similarly, a physician in the Nuclear Medicine Department, Clinical Center, was reported as having a 600 rem exposure to his finger badge. An explanation of this exposure could not be clearly determined and

it is speculated that the film was light struck.

An investigation was conducted as a result of an 86.4 nCi thyroid burden of I-125 in a Guest Worker, Clinical Endocrinology Branch, NIAMDD. The individual performed an iodination without adequate control of airborne radioactive materials and was exposed to an estimated I-125 concentration. The NRC was notified in accordance with the provisions of 10 CFR 20.405.

On October 22, 1974, a report was submitted to the NRC as required by 10 CFR 20.405. It resulted from an 84 nCi thyroid burden of I-131 reported in a Radiopharmacy Technician NM, CC. Breathing zone air samples were not available and there was a possibility that the maximum permissible air concentration may have been exceeded. A thorough investigation indicated that the most probable cause of the uptake was the result of an undetected contamination incident, the result of inadequate personnel monitoring. The calculated exposure to the individual was 943 mrem to the thyroid and 2 mrem, whole body exposure. The circumstances leading to the incident were carefully reviewed and appropriate steps have been taken to prevent a recurrence.

Routine air sampling indicated that a Research Associate, Laboratory of Immunology, NIAID, was exposed to an air concentration of I-125, twice the time modified maximum permissible concentration listed in Appendix B, Table I, 10 CFR 20, resulting from improper use of the iodine containment facilities. It was reported to the NRC in accordance with 10 CFR 20.405.

Quarterly Radiation Committee meetings were attended. Major considerations were: review and reaffirmation of existing policy on use of prophylactic thyroid blocking agents for radioiodine users; approval of new maximum permissible activity guidelines establishing maximum levels of various radionuclides which can be safely handled in the typical NIH research laboratory; review of experimental protocols for ionizing radiation; review of applicants for authorized use; review of radiation incidents; discussion of non-compliant areas; and general discussions of finding and requirements of the NRC.

## 2. Radionuclide Receiving and Shipping

In fiscal year 1975, a total of 9,163 incoming shipments of radioactive materials totalling 122.3 Curies was received. The total cost of such materials was \$1,316,185.38. This represents a 17% increase in shipments over the previous fiscal year.

New procedures for receiving and opening packages, were instigated in response to new Nuclear Regulatory Commission regulations. The new procedures require checking and recording of contamination data on incoming packages and coverage for checking incoming packages for contamination on weekends and holidays.

## 3. Radioactive Waste Disposal

Again, the volume of liquid and solid radioactive waste continued to increase significantly. Six hundred and forty, 55-gallon drums and 10



boxes of radioactive waste were shipped out for burial by Hittman Nuclear Corp. under the terms of an agreement with the Department of Defense. This is an increase of 31% over last fiscal year.

Liquid scintillation vials are picked up weekly for disposal by burial under NIH contract 75-C-18 CC. During the fiscal year, 42,507 trays containing 100 vials each were disposed of, an increase of over 31% above the previous fiscal year.

A ventilated hood was installed in the waste handling area to be used for the storage and assay of volatile radioactive wastes.

The waste compactor was equipped with a HEPA filter to minimize the possible release of infectious or radioactive aerosols to the atmosphere or work environment.

#### 4. Patient Therapies and Diagnostic Studies

Health physics support was given to the Clinical Center in administering therapeutic doses of radiation to 21 patients receiving up to 250 millicuries of I-131. This included radiopharmaceutical assays, assistance in administration of the material, instructions of patient and nursing personnel, contamination control, daily pickup and assay of urine, removal of contaminated linens and other materials, survey and decontamination of room on patient discharge, and records required by the NRC.

#### 5. Laboratory Surveillance

Continued emphasis was given to laboratory and x-ray surveys during FY '75 to assure compliance with NRC regulations, OSHA requirements and NIH policies and procedures governing the safe use of ionizing radiation.

Laboratory compliance and contamination surveys were conducted by Radiation Safety Section staff and by Contract (NIH-75C-217-CC). The contractor conducted 1,489 laboratory surveys. Another 1,448 surveys were conducted by Radiation Safety Program personnel. The total figure is down by about 48% from FY-74 and is attributed to delays in awarding the laboratory survey contract, reduced manpower levels, increased use of radioactive materials, and increased NRC regulatory demands.

As a result of increased emphasis by NRC on the control of airborne radioactive materials, 2,226 air samples were taken from the work area and building exhaust systems, an increase of 271% over the previous fiscal year.

57 diagnostic therapeutic or research x-ray surveys were conducted by Applied Health Physics Inc. (Contract No. 74-C-4111-CC) and 30 surveys or followups were conducted by Radiation Safety Program personnel. In addition, 50 electron microscopes were surveyed for x-ray leakage by RSP personnel. One x-ray diffraction unit was found to constitute a significant radiation hazard and operations were curtailed until appropriate corrective action was taken.

## 6. Personnel Monitoring

Film badge processing (external radiation personnel dosimeters) has been under contract to the Radiation Detection Company since May 1973. Contractor performance has generally been satisfactory and excellent response has been received on requests for immediate film readings.

Individuals on film badges increased from 1778 to 1945, a 9% increase over the previous fiscal year. In addition, 43 employees of the Rocky Mountain Laboratory and two Arizona field stations are also covered on the service.

Thermoluminescent dosimeters were substituted for the film type dosimeter previously used in ring badges. The new dosimeters are more comfortable to the user and there are less difficulties with unidentified or water-damaged dosimeters.

The number of radioassays of urine specimens increased from 1190 last fiscal year to 1260 in fiscal year 1975, an increase of approximately 6%. Specimens were requested of individuals involved in radiation incidents and of those working with certain levels of radioactive materials in compliance with criteria established in the license application and license conditions.

429 investigators and their staff working with greater than established levels of gamma emitting radionuclides were requested to receive whole body counts, a 17% increase over the previous fiscal year.

## 7. Radiation Safety Training

Continued emphasis was placed on Radiation Safety Training. A special effort was made to identify individuals working with radioactive materials not formally trained in the safe handling of these materials. A one-day course, "Radiation Safety in the Laboratory" was presented monthly with 502 NIH employees and 18 guests in attendance.

A two-week course, "Radiological Health for Radionuclide Users" was conducted twice with 119 persons in attendance.

Short one to two hour specialized training sessions were presented to several groups of NIH employees. One-hour presentations were made to Clinical Center nurses as part of their orientation program with 118 in attendance. A two-day training course, "Liquid Scintillation Counting Methodology", conducted by an equipment manufacturer was attended by 36 persons. A similar one-day training course was presented to 23 persons at the Rocky Mountain Laboratory, NIAID. Two separate presentations were made to five physicians and six nuclear medicine technologists of the Nuclear Medicine Department, Clinical Center, to emphasize the importance of using syringe shields and controlling personnel contamination. A one-hour session was presented to 11 members of the nursing staff of the Employee Health Service. A special training session was conducted for the medical and nursing personnel of the Health Catheterization laboratories in the Clinical Center regarding the hazards of x-rays and radioactive materials to which they may be exposed.



Three high school and college students working part-time were given basic radiation safety training in an hour session.

12 nurses on 9 West and eight nurses on 13 West received special instruction on handling patients who received diagnostic levels of radioactive materials.

#### 8. Technical Assistance

The calculated exposures of Nuclear Medicine technologists to selected radionuclides in dosing syringes was verified using calibrated solutions and film dosimetry. Dry samples of the same radionuclides were also measured on an extrapolation chamber to simulate skin contamination. The data was necessary to clarify differences in theoretical calculations presented in the literature. The dose rate at the surface of a syringe loaded with 20 mCi of Tc-99m was found to be around 800 mrem per minute.

Problems with the commercially available syringe shields discouraged routine use by Nuclear Medicine technologists. To overcome these difficulties, several meetings were held with the personnel of the Nuclear Medicine Department, manufacturers, and staff of BEIB, DRS. As a result, a prototype tantalum syringe shield was designed and is in current use. An industrial firm has requested drawings and it is expected to be in commercial production shortly.

A prototype iodine containment facility and adsorption unit was designed by RSP personnel and fabricated by BEIB, DRS. Tests under actual operating conditions indicated it was effective in reducing the concentration of radioiodine released to the environment by 99.8%.

Several meetings were held with personnel from the Bureau of Biologics, FDA and representatives of ESB, DRS, in regard to the location and design requirements of a central iodination facility to serve Building 29. The final plans for this facility, which is to be located in Room 301, were completed and approved.

Final plans for the renovation of the wing of Building 10 (W.R. #342836) were reviewed by this office and were discussed with the Office of Licensing, NRC. Assistance will be provided in inspecting and testing the shielding. The 2,000 Curie Co-60 source will be moved under the supervision of Radiation Safety personnel.

The shielding requirements for Ga-67 and the hazards associated with Xe-127 were evaluated for the Nuclear Medicine Department.

The NRC referred a local hospital for assistance in performing dose calculations for a patient who inadvertently received an overdose of radioactive material.

Radiation Safety in the Physician's Handbook was reviewed for the Clinical Center.

Technical assistance was provided to several researchers with counting problems particularly with double and triple radioisotope labeling experiments; to several local hospitals, university, federal Government, commercial, and NCI contract Radiation Safety Officers on I-125 air sampling and control measures; and to the NHLI, Surgery Branch, in developing a counting method for four different radioisotopes to determine blood flow in three areas of the heart and the cardiac muscle.

Approximately 250 G-M portable survey meters were calibrated, batteries replaced and repaired, if necessary, semiannually by the Institute of Resource Management Inc. under contract NIH 74-C-1140-CC.

#### D. Problems

The most critical problem facing the Radiation Safety Program is the wide disparity between the available manpower resources and the workload required to provide essential services and to assure compliance with the provisions of 10 CFR 19, 10 CFR 20 and the requirements of the Occupational Safety and Health Act.

The imposed manpower ceiling of 18 full-time positions is exactly the same level deemed inadequate by the Chairman of the Radiation Committee in 1968 in his report to the Director of NIH. Since this time, it is conservatively estimated that the workload has increased by greater than 200%. The Radiation Safety Program is a captive of the increased use of radioactive materials as an essential research tool and increasingly more stringent regulations and guidelines of the Nuclear Regulatory Commission.

In 1972, NIH was requested to attend a meeting at the Regional Office of the Nuclear Regulatory Commission to discuss radiation safety program deficiencies and to provide assurances that corrective action would be taken. As a result of a much greater use of contracting, increased use of part-time personnel, increased use of compensated and uncompensated overtime, reorganization and reassignment of program personnel, improved work procedures, increased responsibility on authorized users, a realignment of program priorities, strong support of the Radiation Committee, and the personal sacrifice and dedication of Radiation Safety Program staff, there was a significant increase in the level of Radiation Safety compliance at NIH.

However, the early gains made in lessening the disparity between manpower resources and workload have been negated by program growth and the increasing requirements by the Nuclear Regulatory Commission. Unless there is strong administrative commitment to the principles of the Radiation Safety Guide and the necessary manpower is provided for the Radiation Safety Program to effectively accomplish its mission, the number of radiation incidents and the number of citations issued by the Nuclear Regulatory Commission can be expected to increase. Any significant license restrictions or the possibility of license revocation could be a source of considerable embarrassment to the NIH and NRC. A commitment of unusually high levels of manpower might be required to cope with added restrictions, and the restrictions could seriously jeopardize the effectiveness of the intramural research program.

E. Program Plans

Further use of contract services will be explored. The feasibility and estimated cost of contracting the total radioactive waste handling program is under current review. Improvement in existing contracts as they expire is planned to assure high quality service.

High priority will be given to improved work procedures and more effective utilization of existing manpower resources.

Continued high priority will be given to radiation safety training, surveillance and compliance.

Employee development will be encouraged particularly Adult Education, Upward Mobility College, In-service training and continuing education programs.

Technical assistance will be sought to assure that data processing is fully and effectively used in program management.

High priority will be given to employee morale and the work of the DRS Human Relations Committee.

F. Publications and Patents

A paper entitled, "Radiation Safety in Nuclear Medicine" was presented at the Society of Nuclear Medicine in San Diego, California, June 11-14, 1974, and an exhibit by the same title won a bronze medal in the Technologists' Section exhibits.



## BRANCH PROGRAMS

A. Objectives

The primary objective of the Safety Management Program is to develop and implement a continuing and comprehensive effort toward creating and maintaining safe conditions, procedures, and attitudes as they relate to prevention of all types of accidental injuries, illnesses, or fires.

B. Current Programs

## 1. Accident Reporting, Investigation, and Analysis

In coordination with the Employee Health Service, CC, and other functional areas, the activity is designed to ensure prompt, accurate reporting of accidents; selected investigation of accidents to better define or identify contributing factors and/or to initiate corrective action to prevent a recurrence; and to apply analytical techniques to the accident experience to establish work priorities and to measure relative performance.

## 2. Accident Prevention

In addition to prevention activities resulting from accident investigation, this function specifically applies accident prevention principles, codes, or standards to the work environment. In addition to individual and corporate efforts of SMP staff, coordination is effected with other functional responsibilities, i.e. engineering design, construction, procurement, personnel, policy, transportation, etc.

## 3. Training and Promotion

A function of accident prevention, these activities represent a significant portion of total SMP effort. Primary direction is toward integration of safety needs with other training activities conducted throughout NIH. Promotional activities include distribution of general and specific material on hazards and their control to employees.

## 4. Compensation Officer

Not typically considered a responsibility of Safety Management, a valuable service is rendered to injured employees applying for compensation benefits. Additionally, the Compensation Officer serves as the focal point at NIH for information and advice on requirements of the Federal Employees' Compensation Act, and for education of administrative and supervisory

personnel in requirements and responsibilities under the Act.

### C. Program Progress and Accomplishments

#### 1. Accident Reporting, Investigation, and Analysis

Accident data was transferred from a manual to a computer system. Problems initially encountered in implementing the system, because more data was captured than in the present DHEW system, essentially have been resolved. DHEW machine-readable data can now be provided rather than source documents. More importantly, the SMP system provides a more comprehensive analysis on a timely basis. Such data will be passed on to the management and supervision of high accident producing activities to intensify prevention activities. The change to a computer system necessitated a change of reporting forms. Modification of a DHEW form was developed, approved, and put into service. After several months use, indicated changes were incorporated in a pending revision.

During the early part of the year, staffing permitted a significant expansion of accident investigation activities; however, personnel changes and losses among Safety Specialists have had a serious impact on this activity, although inspections of the major NIH field stations were completed. In spite of restrictions, staff effectively responded on accident reports. Subsequent actions have eliminated serious potential hazards. In light of continuing restrictions on employment, it will be necessary to increase the ability of certain supervisory personnel to adequately investigate a broader range of accidents.

#### 2. Accident Prevention

A comprehensive report, "NIH Fire Safety Posture" was completed and forwarded. It covered all strengths and weaknesses of Bethesda campus buildings related to fire safety. It is anticipated that the report will serve as a basic guide to short and long-range upgrading NIH facilities against extensive loss due to fire. SMP continued to review and analyze Federal and other standards for applicability at NIH and continued to examine the work environment to identify specific instances of non-compliance with existing standards or potential accident-producing conditions. The examination effort was not as extensive as had been planned due to limited resources, although all major field activities were inspected during this year.

A request from the Plant Engineering Branch, later modified to include all of the Division of Engineering Services, directed considerable staff time toward development of an "Industrial Safety Guide." Much material has been developed to date, but there is a major problem of acceptable format. Construction/alteration review and approval continued.

Work was initiated, in conjunction with the Division of Contracts and Grants, OD, to develop an effective and acceptable "safety and health" clause appropriate in certain classes of contracts. DHEW policies requiring such a clause were originally issued in 1968 and changes such as the Occupational Safety and Health Act of 1970 have made certain of the provisions obsolete. Unofficially, the Director of Safety, DHEW, indicated



a willingness to consider any material developed at NIH as a Department-wide substitute for the existing policy. Although originally felt to have limited application, it now appears a broadly coordinated undertaking will result.

### 3. Training and Promotion

SMP representation was regularly included in all basic Supervisory Training conducted at NIH including routine new employee orientation for Clinical Center and ADA personnel. An eight-hour review of fire prevention codes was presented to approximately 40 DES engineering staff. In conjunction with the Training and Development Branch, Division of Personnel Management, safety material was provided for inclusion in secretarial training.

Changes in provisions of the Federal Employees' Compensation Act necessitated a major training and orientation effort for supervisory personnel in ADA and DES, as well as timekeepers in several areas.

Several releases of "Spot Hazards" were prepared and distributed.

The Supervisor's Guide to OSHA was prepared and distributed. It identifies workplace standards promulgated under the Occupational Safety and Health Act considered applicable to the NIH environment and outlines basic supervisory roles. This simplified description of complex standards will measurably aid efforts toward more complete compliance.

A "Safety Guide for Contract and Project Officers" was prepared in draft and reviewed by interested or affected staff. Work was temporarily halted when some questions associated with the basic provisions needed further development by the Division of Contracts and Grants. This project will be completed by mid-FY 1976.

Three slide/cassette programs were completed: Research Laboratory Safety, Safe Driving, and Workman's Compensation. Copies were provided to all major field locations and DHEW. The original artwork for the Research Laboratory Safety series was released to the National Safety Council for production and distribution through their facilities. This is the first time a cooperative undertaking with the Council has been brought to a satisfactory conclusion.

Training was provided to other government personnel for qualification as road test examiners on request by the Civil Service Commission.

Developing and establishing training needs identified by the NIH Biohazard Committee was initiated.

In addition to approximately 40 mandays of career training, the staff participated in presentations to personnel and/or students of the University of Maryland, Georgetown Medical School, University of Minnesota, and local research organizations.

#### 4. Compensation Officer

The total claims for compensation filed during CY-1974 did not vary significantly from the previous year, but there was an atypical up-swing during the last quarter of FY-1974. This is largely due to the changes in the Federal Employees' Compensation Act which now permits continuing an employee in a pay status up to 45 days for loss from work as a result of a traumatic injury. Previously, "lost time" injuries involving less than 21 days, required a three-day waiting period in a non-pay status. Participation with the Division of Personnel Management in the "Hire the Handicapped Program" resulted in reassignment of several employees who otherwise would have been retired on compensation disability as a result of work-associated injuries or illnesses.

#### D. Problems

Many of the attempts to achieve compliance with applicable standards were thwarted by the lack of adequate research space. It is nearly impossible to provide the needed ventilation or building renovations without significantly disrupting ongoing research. While one may argue the corridor must be "clean," there is clearly a problem of diminishing returns if already congested laboratories are expected to absorb even more equipment. This problem is certainly not new to NIH and is subject to decision controls external to NIH. SMP will continue to seek alternatives which will provide improvement. Some of the larger, semiroutine labs may lend themselves to industrial work-flow techniques which typically have not been considered in the research environment.

A complete report of crowded and cluttered conditions in Building 10 was completed and forwarded. While some areas subsequently showed improvement, the overall impact of this project was not as effective as was hoped. Continued space shortages coupled with restricted manpower in the central services, seriously affects quick resolutions of this long-stand problem.

The present size of the staff does not permit adequate performance in the wide range of the responsibilities associated with the program. Staff shortages require a critical evaluation of priorities.

#### E. Program Plans

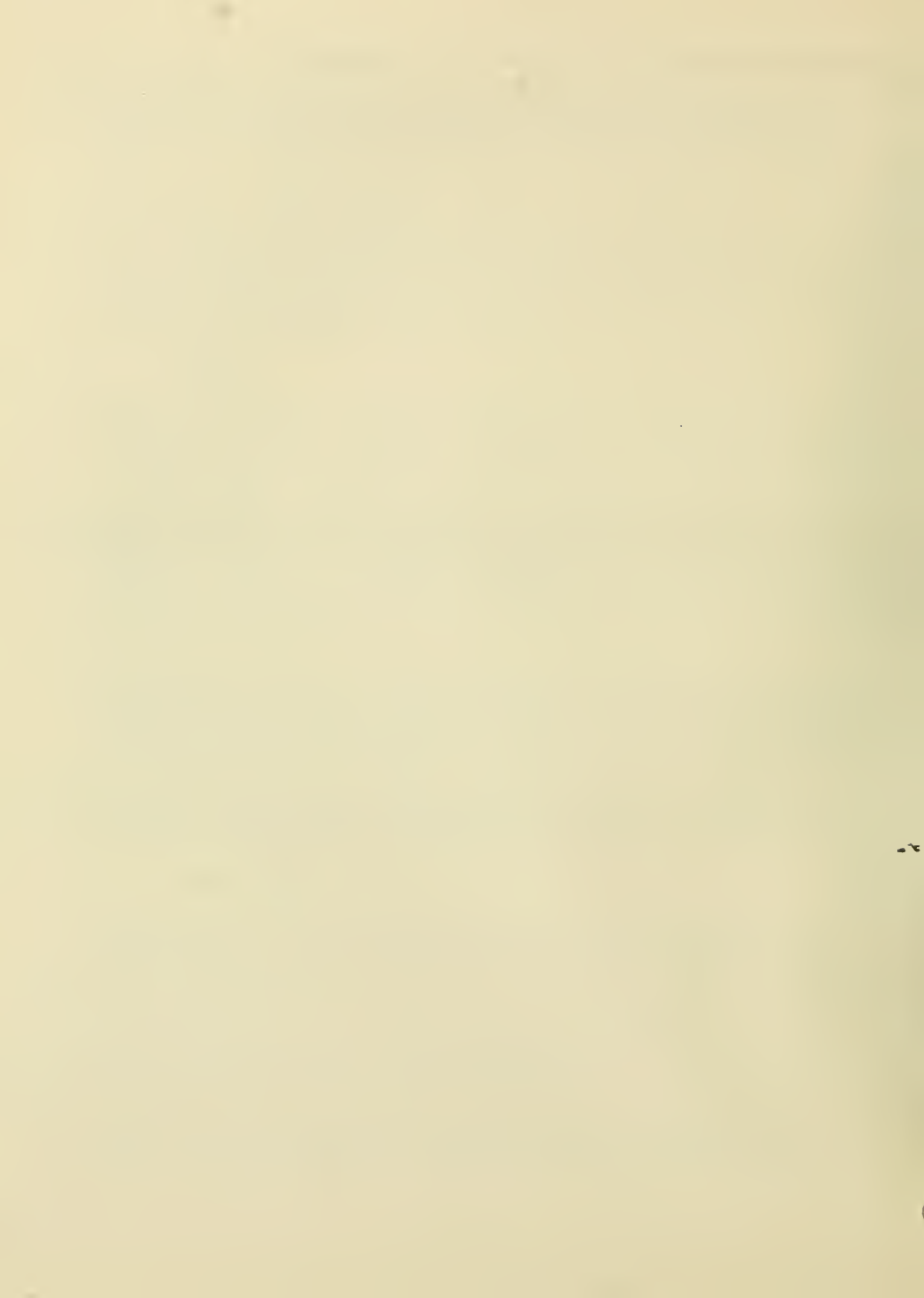
Computer-based accident data will be used as a more timely management information system than was possible under the manual procedure. Data analysis will also improve techniques for determining program priorities or areas of concentration.

A comprehensive analysis of safety education and promotion needs will be completed and translated into a coordinated program. A safety awareness program, "Life is Fragile" will be implemented.

In conjunction with the Supervisor's Guide to OSHA, a self-inspection program will be initiated as one means of extending compliance efforts. In addition, methods for possibly utilizing other personnel for certain

classes of inspection and reporting will be investigated.

Although Program objectives will be performed, the order of priorities and staff assignment will depend on the nature of the organization of the Environmental Health and Safety Program.



DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1974, through June 30, 1975

LIBRARY BRANCH

Ruth C. Smith, Chief

I. SUMMARY

The Library Advisory Committee met three times during the year. Dr. Philip McMaster, NIAID, was appointed Chairman in February replacing Dr. John S. Finlayson, BB, who had served in that capacity for several years. At the same time the Committee was enlarged to 17 members with representation from all I/D's.

On February 24, the Supreme Court, by a tie vote four to four, with Justice Blackmun disqualifying himself, affirmed without opinion the U.S. Court of Claims decision in the case of Williams and Wilkins vs. the U.S. that large-scale unauthorized photocopying and free distribution of copyrighted medical journal articles by NLM and the NIH Library are not copyright infringements.

A memorial for Dr. Henry W. Scherp was presented to the Library in the form of monies to be applied for the purchase of books and journals for the Library collection in subject areas of interest to NIDR.

A duplicate Library catalog was established on the Lower Level for use in proximity to the book collection.

Effective November 1, the Technical Services Section was reorganized into two units, the Monographs Processing Unit and the Journals Processing Unit replacing the Acquisitions and the Cataloging Units. Functions and duties were realigned to eliminate much duplication of procedures.

The Library became a member of the Ohio College Library Center's shared cataloging automated network system through the Federal Library Experiment in Cooperative Cataloging. On-line access to the cataloging data-base in Columbus will significantly contribute to more effective performance of technical services.

After inspection and analysis of major automated library circulation systems, the decision was made to adopt the University of South Carolina Library system. The designer of the system visited the Library as consultant to advise with the Library, DRS Management Analysis Office and the DCRT representative. The PDP 11/40 minicomputer to be used in the Library underwent tests in DCRT. The project is in progress to convert the Library's bibliographic records for books in the collection into machine readable form.

A nonprint collection was organized. Current audiocassettes, tapes and slides were added to previous microform holdings and are available for use in the Library or for loan. Newly acquired nonprint items are included in the monthly memorandum of additions to the Library.



The Branch Chief was named the Division of Research Services Chairman of the 1975 Combined Federal Campaign. The Assistant Chief served as DRS Coordinator of the Drive.

The Library prepared exhibits in connection with each NIH minority cultural week celebration for display in the outside corridor. The Branch Chief continued as a member of the NIH Minority Cultural Program Committee.

The Branch Training Program provided training for individual employee development and more effective use of the employee in the Library.

At the request of the National Cancer Institute, the Frederick Cancer Research Center at Ft. Detrick was visited five times during the year in relation to monitoring the library services provided by the contractor.

## II. BRANCH PROGRAMS

### A. Objectives

The primary mission of the Library Branch is to operate an efficient, comprehensive library in support of NIH scientific, medical, and administrative programs. Activities of the Library include selection, acquisition, organization, maintenance, and circulation of literature pertinent to the programs; operation of a photocopy service; provision of interlibrary loan service; provision of informational, reference, and bibliographical services; provision of Library services advisory assistance; and provision of a translating service for foreign scientific and medical literature. To fulfill its mission, the Library is responsive to changing literature needs of the NIH investigators, is knowledgeable of current developments in manual and machine methods of communication and information retrieval, and is alert to adjustment of procedures for improved Library services.

### B. Current Programs

#### Technical Services

The Journals Processing staff procures journals by purchase, gift and exchange which have been selected as pertinent to the scope of the Library. The staff organizes and processes the journals for inclusion in the collection and maintains accession records using manual and automated systems. It also prepares completed volumes for commercial binding.

The Monographs Processing staff procures monographs and similar literature which have been selected as pertinent to the scope of the Library. The staff catalogs, analyzes for subject representation and processes these accessions for inclusion in the collection using manual and automated systems. It also maintains the Library's catalogs and prepares listings for the monthly memorandum of additions to the Library.

#### Readers Services

The Circulation staff provides a charging system, making available books and journals. The staff issues Library Identification Cards; operates the Library's security system; provides an overdue recall system; and makes assignments to locked study carrels.

The Stacks and Copy Service staff maintains the stacks, carrels, reference and Reading Room areas and shelves books and journals to facilitate access by the Library clientele. A copy service is provided which allows greater use of the Library's journal collection.

The Interlibrary Loan staff obtains from other libraries literature required by NIH investigators which is not included in the collection.

The Readers Services Section is responsible for developing, maintaining, and servicing a collection of library material in nonprint media pertinent to the scope of the Library and for providing equipment for its use.

## Reference and Bibliographic Services

The Library Services Adviser Program provides an integrated response to the information needs of the NIH scientific community. This may consist of utilization of external resources in addition to the resources and services available in the NIH Library, such as specialized information centers, computerized information retrieval systems, and clearinghouses. The Reference staff supplies ready response to questions, verifies citations, and compiles short reference lists upon request. Its staff receives inquiries at the Reference Desks in the Upper and Lower Level Reading Rooms and by telephone. Reference Librarians answer difficult reference questions and compile literature searches as requested and maintain the collection of basic Reference Books. Professional staff provides bibliographic assistance with experienced searchers to conduct requested medical, chemical and biological computer searches through National Library of Medicine's MEDLINE, Chemical Abstract's Chemical and Biological Activities (CBAC) and Biological Abstract's BioSciences Information Service (BIOSIS). Professional staff also selects books, journals and other literature for the Library collection by continually searching for literature pertinent to the scope of the Library.

### Translating Service

The Translation staff provides oral, recorded and written translations as requested. Oral translations are emphasized in-house. Written translation service is provided through contractual firms with quality control maintained by the Library.

## C. Program Progress and Accomplishments

### Technical Services

A reorganization of the Technical Services Section was effective November 1, 1974. The Journals Processing Unit and the Monographs Processing Unit replaced the former Acquisitions Unit and the Cataloging Unit in order to eliminate duplication of procedures. Reorganization of functions and duties necessitated the rewriting of all position descriptions, posting of six realigned positions according to the Merit Promotion Plan and an intensive on-the-job training program for all Section employees.

The Library became a participant in the Ohio College Library Center's shared cataloging automated system through the Federal Library Experiment in Cooperative Cataloging. The Library's staff has access and makes input to cataloging and acquisition data in the computer in Columbus contributed by 700 or more libraries. Catalog cards for monographs are obtained through this system.

A duplicate Library catalog was established on the Lower Level near the monograph collection to provide needed information on location. Duplication of the cards was performed by a contractual firm.

The second edition of Current and Noncurrent Journals in the NIH Library was issued in 1974 (for administrative use). Arranged alphabetically by title, it includes for the first time complete holdings for all journals in the Library's collection. Due to the increased size of the second edition, the subject section of the first edition was eliminated.

#### Readers Services

Plans were completed for the implementation of an automated circulation system which will provide a more efficient service to the NIH community and better control of the Library's collection. Major automated library systems around the country were inspected and studied and after discussions with DRS Management Analysis Office staff and DCRT, it was concluded that the circulation system used by the University of South Carolina met the needs of the NIH Library. A PDP 11/40 minicomputer delivered the last of April was tested in DCRT prior to placement in the Circulation Unit. Mr. Kenneth Simons, designer of the system, visited the Library and made valuable suggestions especially relating to layout and system adaptation. The project of converting the Library's bibliographic records for books in the collection to machine readable format is underway. Mr. Michael Kremer, DRS Management Analysis Officer, and Mr. James De Leo, DCRT, are collaborating with the Library in implementing the system.

Installation of a new copier has improved the important self-service to NIH investigators and supporting staff.

The Library's collection of microforms including microcards, microfiche and microfilms has been listed by the nonprint Librarian. Guidelines for processing each type have been developed and nonprint items newly acquired and cataloged are included in the Library's monthly memorandum of new accessions. A modest number of current videocassettes and audiotapes have been acquired for use in the Library or for loan. An article on the service "NIH Library Offers Use of Microforms to Save Journal Shelving Space" appeared in the December 17 issue of the NIH Record.

#### Reference and Bibliographic Services

MEDLINE bibliographic search requests completed for calendar year 1974 amounted to 7220, representing an increase of 1715 searches (23.7%) over the number of searches performed in 1973. The number of requests for searches in the field of chemistry through Chemical Abstracts automated CBAC service and in biology and related subjects through Biological Abstracts BIOSIS system were substantially the same as for the previous year.

#### Translating Service

Requests for oral, recorded and written translation services continued at the same level as last year.

## Training

The FY 1975 Branch Training Program provided individual employee development in the present job and more effective use of the employee in the Library. Employee training was completed in academic, professional, administrative, technical and in-Library courses and workshops. Two employees continued in the Adult Education program, one in the regular program, the other in a special training course. Three employees were enrolled in the NIH/FCC Upward Mobility College, one in Federal City College and one in the University of Maryland.

## Exhibits

Exhibits prepared by the Library staff and displayed during the year covered the following topics: Radiation Safety and Nuclear Medicine (prepared by Radiation Safety); Asian-American Cultural Week; Spanish-American Cultural Week; World Population Year 1974; Black History Week; CANCERLINE Bibliographic Service; National Library Week; BEIB Service (prepared by BEIB); Native American Week; and Governmental Technical Reports in Relation to Biomedicine. Assistance was received from the Medical Arts and Photography Branch.

## D. Problems

Downtime and poor quality of two of the photocopy machines continue as problems. One new machine has improved the situation; the acquisition of two additional machines replacing the old should eliminate this problem.

A careful examination and weeding of the monographs collection remain to be accomplished as soon as the Scope and Coverage Statement is completed.

The soaring cost of journal subscriptions has necessitated a reexamination of the Library's acquisitions policy. Second copies of some journals have been eliminated through the concerted efforts of the Library staff and the Library Advisory Committee.

## E. Program Plans

Implementation of an automated circulation control system developed by the University of South Carolina will be completed. The new system, using a minicomputer and light pen technology, will provide more efficient service to Library clientele and improved control of the Library's collections.

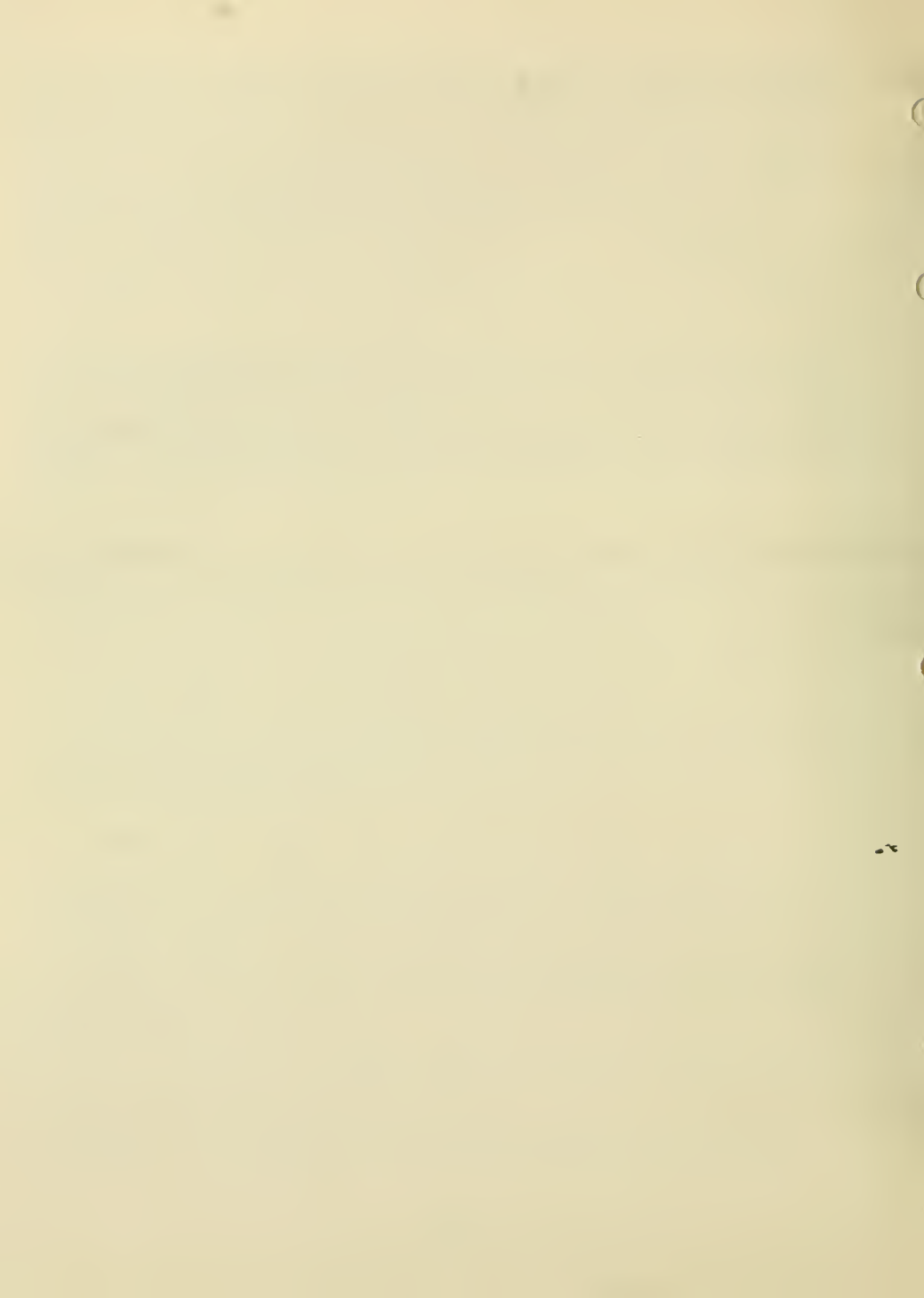
An analysis of additional applications of the minicomputer to other Library operations will be completed with the assistance of the DRS Management Analysis Office and DCRT staff.

Continued expansion of the nonprint media collection is planned, based on specific requirements of NIH investigators.

Conversion of the subject headings used in the Library's catalogs for identifying and locating medical books and journals to the specialized







DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1974 through June 30, 1975

MEDICAL ARTS & PHOTOGRAPHY BRANCH

Mr. Arthur F. Moore, Chief

I. SUMMARY

Demands for MAPB services increased approximately 25 percent in FY 1975. Physical consolidation of the graphics activities has satisfied the need for complete unity in graphics and statistical art preparation. Delivering finished work has accelerated. Medical illustration demands remain normal. Delivery of scientific photography has been reduced from 15 days to seven. Work has been done to establish graphic standards for statistical materials produced by the Branch. This is a forerunner of a continued drive to establish a unified visual communications system for the NIH. With new equipment and wider use of contract service, the Branch continues to broaden its skills and meet increasing demands for service.

## II. BRANCH PROGRAMS

### A. Objectives

The objectives of the Branch are to provide consultation and production services to the NIH; to visually communicate program effort and research results; to provide knowledge, skills and techniques in visual design, medical art, applied arts, still photography and cinematography for solving problems of recording, communicating and presenting research activity; and to investigate, develop and apply new visual techniques.

It is also the objective of the Branch in meeting NIH research program demands to provide professional services, competitive with commercially obtainable services at the lowest possible cost, and to develop specialized capabilities, particularly in graphic presentation, still photography, cinematography, and medical arts, tailored to NIH needs.

The Branch monitors procurement of art and photography services by outside contract, serving as a technical adviser in obtaining needed additional services at the lowest cost consistent with high quality.

### B. Current Programs

Programs of the Branch are still and motion picture photography, including photomacrography, photomicrography, cine photomicrography, high-speed cinematography, general photography, and related laboratory services; visual arts production including publications design and general graphics; visual aids including slides, vu-graphs, and other projectables; animation artwork; technical, general and medical illustration; exhibit design; statistical drafting display charts, and medical models.

### C. Program Progress and Accomplishments

1. Increased demands for services were made of the MAPB this year, climaxed by the intense activity created by the first NIH Alumni Homecoming, Public Open House, and the Bicentennial celebration.

2. In FY 1974, the General Illustration Section was renamed the Design Graphics Section and its three Units were reduced to two. However, the physical joining of the drafting and graphics operations did not take place until early FY 1975. The reorganization has been an unqualified success. The unit functions quickly and efficiently and is capably handling a constantly increasing workload; and unity of preparation has been accomplished. With the addition of electronic production of typography, the unit has been able to broaden its capabilities and reduce turn-around-time.

3. In the design area, there was a substantial increase in demand for services. As an example, 21 of the 23 major exhibits displayed at the Alumni Homecoming, Open House, and Bicentennial celebration were designed and construction was supervised by this Section.

4. The NIH demand for medical illustration remains normal and the Photography Section has been able to keep abreast of a 20 percent increase in service by use of new equipment, improved management and wider use of contract services. In FY 1974, delivery of scientific photography took 15 days, which was excessive. This year, turn-around-time, as forecast, has been halved.

5. The Branch, through extensive review, has identified the graphics design company with the concept and expertise to research and develop a coordinated visual communications system for the NIH. As a start, work has been done on establishing standards for graphically rendering statistical material (charts, graphs, tables) produced by the MAPB for publication and projection.

6. The Branch lost one person, increased its use of outside contract services by 26 percent, reflecting an increase in demand for services.

7. Thirty-two employees spent 1332 hours attending 43 training courses at a cost of \$4,359.00.

8. The Branch has concluded one year of a two-year negotiated agreement with AFGE Local 2419. Relations have been smooth and without incident. The President of the Local, an MAPB employee, was elected for a second term.

9. An ongoing program of familiarization of Branch employees with EEO goals continues. Seven employees attended the two-day DRS-EEO Seminar in November.

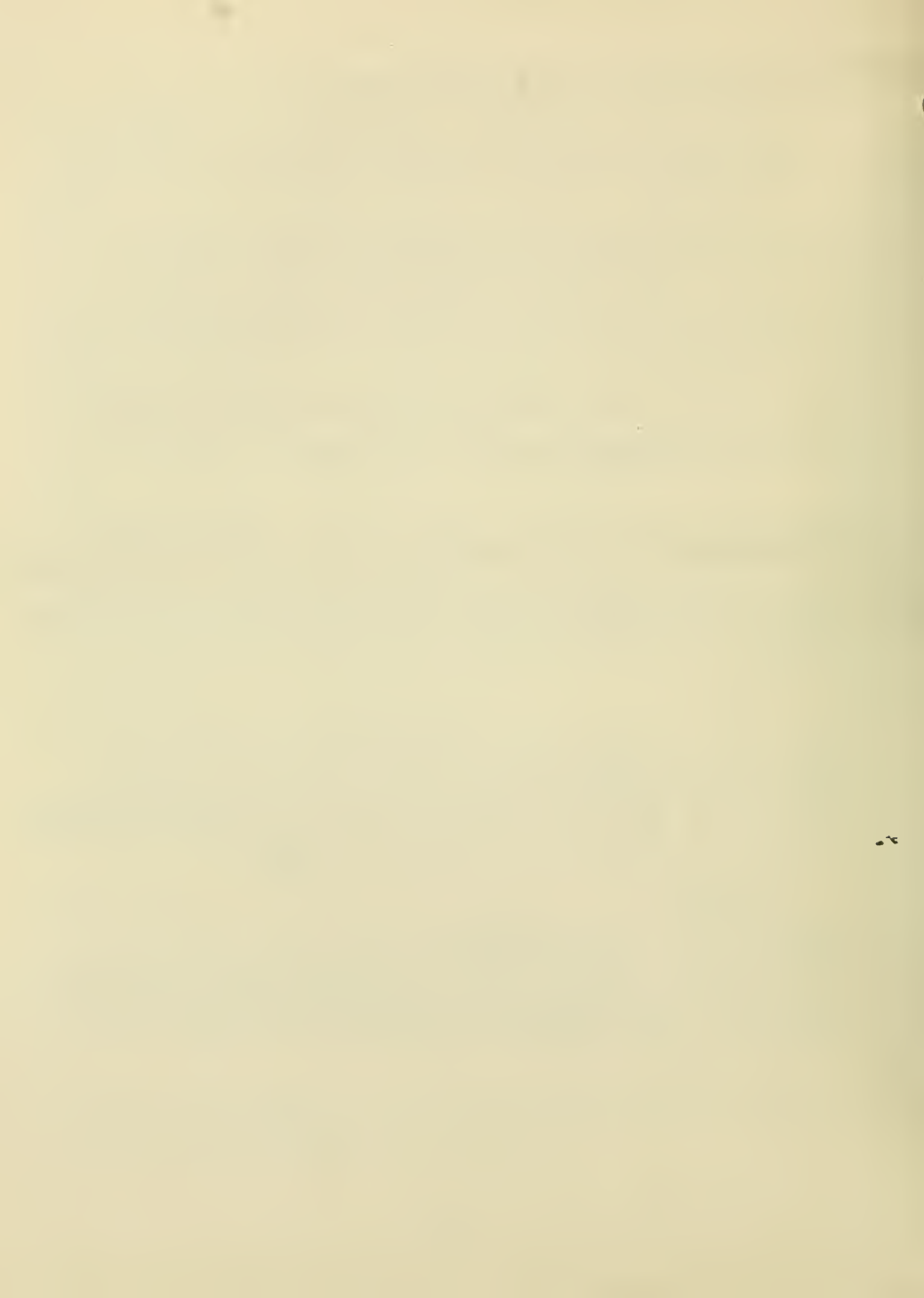
#### D. Problems

There remains a critical need for the NIH community to allow more lead time for planning and execution of audio-visual material. All too often, the thoughtless and needless demands for rush jobs deprives the majority of NIH requesters the reasonable service they deserve. The Branch has extensive expertise in planning and conversion of raw data into effective multi-media presentations. This counsel is readily available in all areas of MAPB, or on location, and should be used earlier and more frequently.

#### E. Program Plans

The Medical Arts & Photography Branch will pursue the development and implementation of a systems approach to upgrading NIH visual communications. It will continue to improve, enlarge, and extend its services and will seek more effective ways to acquaint the NIH community with its skills. The Branch will continue to emphasize the necessity of early counsel and planning for optimum results.





DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

July 1, 1974 through June 30, 1975

Veterinary Resources Branch

Dr. Robert A. Whitney, Jr., Chief

I. SUMMARY

The Veterinary Resources Branch provides NIH investigators with living models and life support systems for biomedical research. The Branch also provides facilities and services related to the use of these models and systems.

VRB service functions continued to increase to meet demands of expanding intramural BID programs, although Branch personnel ceilings have been reduced 18 percent over the last seven years. Increased service with decreased personnel was accomplished by extensive use of overtime, improved animal production methods, automated processing of glassware and production of media, limited use of temporary positions, and contracting.

The VRB rodent breeding colonies were designated as a World Health Organization collaborating center in recognition of their importance as an international genetic repository. A committee of the National Research Council reviewed this effort and recommended that it be removed from the Service and Supply Fund and be given separate funding. More breeding nuclei were provided this year to start new colonies outside NIH than have been requested in previous years. VRB colonies now serve as the genetic base for most NCI contract programs as well as the Frederick Cancer Research Center. The Catalogue of NIH Rodents was distributed internationally to over 1,000 researchers and specialists in fields of laboratory animal science. Twelve new rodent strains were added to the collection.

Open or complete disclosure formula rations for laboratory animal feeds developed by VRB permit competitive bidding for feed contracts, thereby reducing prices. Savings this year from conversion to open formula rations are estimated to be over \$100,000 compared to the estimated costs of closed formula rations purchased under noncompetitive contracts.

Pathogen-free rabbit and guinea pig colonies were successfully initiated this year. Nucleus colonies of guinea pigs were hysterectomy derived and established in the barrier in a clean, conventional area. An autoclavable diet for guinea pigs was successfully tested. Hysterectomy derivations were completed to establish all VRB rabbit strains in a new nonbarrier facility. They were foster nursed by SPF Edgewood Arsenal rabbits.

A list of diseases for which NIH animals will be monitored was prepared. A system for carrying out the required tests is being developed. It is anticipated that notification of the microbial status of VRB animals will accompany all animals when shipped.

Total issues of VRB-produced rodents and rabbits remained about 500,000, comparable to FY 1974. The use of animals produced on contract decreased from over 130,000 in FY 1973 to about 70,000 this year.

The Perrine Primate Center, established by DRS in FY 1974, is now stocked with 350 rhesus breeders and 75 squirrel monkeys. Two contracts were awarded in June 1974 for additional rhesus monkey breeding colonies. By FY 1978, these three DRS breeding operations are expected to supply 1,000 rhesus and 100 squirrel monkeys annually for intramural research.

Tissue culture and media production increased 7 percent. Blood agar plates were issued at a 7 percent increase also. Glassware issues increased slightly over last year, as did the use of disposable supplies. Surgical activities and support stabilized at 800 procedures per year. Surgical facilities were relocated from Building 28 to Building 14E, increasing capacity for surgical procedures.

With Phase I renovation of Building 14D completed, isolated facilities are available for holding 1,000 nonhuman primates. Over 1,900 primates will be held in this building on completion of Phases II and III renovations.

The Branch continues to produce colony reared dogs and goats and maintains a canine blood donor colony. The long-term holding of ungulate animals under investigative study, and the procurement, quarantine, and conditioning of nonhuman primates, cats, and ungulates continues. Production in most areas is projected to be above FY 1974 levels. Emphasis is being placed on the development of breeding programs to supply quality animals for research. Burro breeding is being developed, and the foxhound colony is being enlarged. Random source dogs are no longer procured.

The Animal Disease Investigation Service was reorganized to ensure rapid response to requests. The number of calls made to the BID's remained at last year's level of approximately 180. They involved consultative, diagnostic, and therapeutic activities and included rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls are varied and involved all Institutes. This service has been well received by the BID investigators. It has been mutually beneficial to the investigators and the VRB professional staff by providing a means of communication between groups.

## II. BRANCH PROGRAMS

### A. Objectives

The primary objectives of the Veterinary Resources Branch are:

1. Issuance of research animals, animal biologics, tissue cultures, tissue culture media, bacteriologic media, and laboratory glassware.
2. Maintenance of a centralized genetic repository of valued animal strains for the scientific community.
3. Provision of facilities and professional staff for experimental surgery to include postoperative care, roentgenography, and other special procedures.
4. Maintenance of animals during experimentation and collaborative research support.
5. Acquisition of information, through research, on animal health, care, and husbandry, and identifying animal models for human diseases.
6. Provision of consultative services on animal health and husbandry, use of experimental animals, tissue cultures, and bacteriologic media.
7. Establishment and supervision of production colonies of animals that are not commercially available to the NIH community.
8. Monitor procurement of animals, environmental housing, and biologicals used in biomedical research.

### B. Current Programs

#### 1. Research Animal Production

Rodents, rabbits, dogs, cats, and primates are bred and reared in the Branch's colonies. Some are characterized genetically and some are microbiologically defined. Care is taken to maintain the genetic integrity of inbred strains and minimize inbreeding or random bred stocks. Germfree and specific pathogen-free (SPF) rodents are produced for intramural research programs requiring them and for replacement breeders to enhance the health status of production and genetic colonies. Rhesus monkeys are bred to provide either timed pregnant females or neonates for intramural research.

#### 2. Research Animal Procurement and Conditioning

Nonhuman primates, dogs, cats, ungulates, and feral animals are purchased and conditioned. These animals are not well defined genetically or microbiologically. Although they are of lower quality than NIH-bred animals, they are satisfactory for certain studies. These animals are quarantined prior to release for use in research programs. During the quarantine period they are given appropriate immunization, tested for a variety of infectious agents, and are treated medically as required.

A colony of blood group CEA 1, 2, and 3 negative canine donors is maintained for the production of normal canine blood for research use. Ungulate animals are maintained for the production of antisera, normal blood, or tissue specimens.

Facilities are provided for investigators to perform experimental surgery on ungulate animals. They include modern equipment for restraint, anesthesia, and physiologic monitoring under aseptic conditions. Postoperative care is provided and radiographic facilities are available.

Ungulates are held under observation for NIH investigators during investigative studies. Physiological sampling and specimen and collections are provided in association with these studies.

Noninbred rodents and rabbits are procured through contracts to supplement in-house production. They are delivered directly to NIH investigators. Quality control of these species is maintained through monitoring of the various producers' facilities and operations by Branch staff members.

### 3. Tissue Culture and Media Production

Several continuous cell line tissue cultures are maintained, propagated, and produced in large volumes to supplement I/D requirements not met by commercial sources or individual laboratory preparation. Media for the culture of bacteria, fungi, and tissue cells are produced to meet the needs of NIH investigators. A stringent quality control program insures that only high quality products, free of contamination and true to formulation, are issued. As a service to investigators, valuable cell lines are frozen and stored for long-term preservation.

### 4. Processing Laboratory Glassware, Animal Cages, and Miscellaneous Items

Laboratory glassware is decontaminated, sorted, cleaned, inspected, plugged, wrapped, sterilized, and issued to NIH investigators. The overall operation includes processing of used glassware received from investigators and the introduction of new glassware from replacement stock. In addition to cleaning animal caging for its own programs, the Branch furnishes cagewashing services to investigators in the Clinical Center and the Building 14-28 complex. Clinical Center rubber-backed carpets are also washed. A service is provided for ethylene oxide sterilization of heat labile patient and laboratory equipment from the Clinical Center and other I/D's.

### 5. Animal Biologics Production

A dog blood donor colony is maintained for the production of Canine Erythrocyte Antigen (CEA) 1, 2, and 3, formerly A-negative, blood for research use. Ungulates are maintained to produce a variety of antisera, blood, and tissue specimens for investigators.



## 6. Genetic Repository and New Animal Models Program

Genetically defined rodents that are valuable models in biomedical research are derived and maintained to support I/D requirements and serve as a genetic repository for the international scientific community.

## 7. Experimental Surgery, X-ray, and Related Activities

The surgical facilities are primarily available for the use of BID investigators however, frequently, surgery is performed by staff veterinarians in support of BID programs in the development of surgical animal models. In addition, staff veterinarians provide surgical and clinical veterinary care to laboratory animals as an essential part of their responsibility to assure optimum health of these government-owned animals. Assistance to BID investigators is continuously provided in anesthesiology, surgical support, diagnostic radiology, and postoperative care of animals.

The number of surgical procedures has stabilized at approximately 800 per year and the facilities are being used at maximum capacity. An increase of 10 percent is projected next year since the surgery unit relocated from Building 28 to Building 14E, permitting more surgical space. The surgery unit maintains a 500 milliamperage radiographic unit with fluoroscopy which adds an improved service for research and clinical support to laboratory animal medicine.

Experimental surgery continues to be complex with numerous thoracic, cardiovascular, and abdominal procedures demanding a high level of technical support. Professional and technical assistance to BID investigators increased, which resulted in improved surgical animal models and veterinary medical care.

## 8. Experimental Animal Holding

Dogs, primates, ungulates, and germfree rodents are held for varying periods of observation while under test by NIH investigators. Provision is made for physiological sampling and collection of specimens.

## 9. Disease Investigation, Research, and Quality Control within VRB

The professional staff consists of persons trained in general clinical veterinary medicine and specialists in laboratory animal medicine, pathology, microbiology, epidemiology, nutrition, animal behavior, genetics, and animal husbandry. All efforts are oriented toward improving the Branch's programs by gaining new knowledge through research and monitoring the quality of procured and produced animals.

## 10. Consultative Services

Information and assistance are available to NIH investigators for solving problems relating to animal experimentation, health, care, and husbandry. Through the Animal Disease Investigation Service (ADIS) "house calls" are made to the I/D's to provide investigators with clinical veterinary services for their research animals. There is also a program to furnish each I/D a comprehensive review of its animal care programs with evaluations and recommendations

for improvement. Consultative services on use of tissue cultures and microbiologic media are available.

## 11. General Support and Management

These basic programs listed above are also supported by Branch-wide administrative and management staff and transportation/delivery service.

### C. Program Progress and Accomplishments

#### 1. Rodent and Rabbit Production

About 500,000 VRB-produced rodents and rabbits were issued to investigators, equivalent to the number produced last year. Guinea pig, rabbit, and hamster production decreased; rat and inbred mouse production remained unchanged, but there was an increased requirement for and production of VRB, noninbred mice. The total demand for VRB strains and stocks of mice was not satisfied because of limitations on current production levels due to personnel ceiling restrictions. Approximate animal issues were as follows:

Inbred mice	230,000
Noninbred mice	170,000
Inbred rats	10,000
Noninbred rats	25,000
Inbred guinea pigs	15,000
Noninbred guinea pigs	11,000
Hamsters	2,000
Rabbits	2,000
Germfree rats	550
Germfree mice	750

The Frederick Cancer Research Center (FCRC) continued to rely on VRB foundation colonies as the genetic base for their rodent colonies. Pedigreed mouse and rat strains were supplied from VRB barrier-maintained colonies. However, preparations were made to supply them germfree pedigreed stock. VRB has also assumed the responsibility of maintaining the genetic base for a variety of other NCI contract programs requiring germfree pedigreed stock.

A breeding nucleus of hysterectomy derived guinea pigs was established in a clean conventional area. A nucleus of guinea pigs was also established in the barrier. Foundation stock for the inbred strains will be hysterectomy derived and foster nursed by those animals to create pathogen-free foundation and expansion colonies.

Efforts continued to develop acceptable pathogen-free rabbits. VRB strains were hysterectomy derived and foster nursed in a clean conventional area by pathogen-free stock provided by Edgewood Arsenal. The rabbits remain free of the usual pathogenic organisms, including *Bordetella* and *Pasteurella*; however, mortality is excessive from nonspecific gastrointestinal problems. "Pathogen-free" rabbits were received from two other sources with the hope that their gastrointestinal flora would eliminate the enteric problem. The plan was thwarted because in both cases the rabbits were found to harbor pathogenic organisms.

Several changes were made in the conventional guinea pig colonies to increase production and enhance the quality. Major accomplishments were the elimination of vegetable supplementation to the inbred pedigreed colonies and the successful testing of an autoclavable diet. A shorter breeder rotation system was initiated and surveillance of breeder performance and replacement was intensified. Inbred guinea pig production began to increase in the last quarter following a decline earlier that contributed substantially to a revolving fund deficit.

The reorganization of the Small Animal Section was implemented with the establishment of a WS supervisor for each building, a cagewash unit, an ordering and contracts office, an administrative assistant, and a professional services group. This concludes a two-year process. It was immediately apparent following the change that the new supervisors and improved organization create a potential for greatly improving the effectiveness of the section.

## 2. Large Animal Production

The conventional canine breeding colony currently consists of 162 bitches and 12 dogs. Culling continues to be directed towards eliminating poor producers and animals with hip dysplasia. The inbred foxhound colony consists of one English and three American (two Walker and one Trigg strain) foxhound lines. Development of these lines is being directed principally towards providing a genetically uniform research dog for NIH investigators by eventually cross-breeding the lines.

A contract was established to breed and provide purebred foxhounds for NIH research at a rate of 500 per year. Availability of purebred stock from the NIH Animal Center and contract sources has eliminated the need to rely upon random source foxhounds and random source mongrel dogs as standard NIH research animals.

The cat breeding colony was terminated during FY 1975.

The goat breeding herd was expanded from 16 to 20 does and 2 bucks. Goats produced from the breeding herd will be held until approximately one year of age before issue.

## 3. Nonhuman Primate Production

The Perrine Primate Center was established by DRS in FY 1974. The facility has been managed by VRB since its establishment and is currently stocked with 350 rhesus and 75 squirrel monkey breeders. These colonies are planned to be maintained at 700 and 150 adult breeders, respectively. Two contracts were awarded; one to Hazleton Laboratories and the other to Gulf South Research Institute in June 1974, to establish 700 additional rhesus monkey breeders. As of June 1975, VRB expects to have supplied the necessary adult breeders to the contractors. By FY 1978, these DRS breeding operations are projected to supply 1,000 rhesus and 100 squirrel monkeys annually for intramural research.

Cutbacks in rhesus monkey exports from India in 1974 prompted VRB to initiate domestic breeding programs. Further cutbacks are expected in FY 1976. Procurement and availability of most New World monkeys is virtually nonexistent. Supplying monkey models for research appears to be largely dependent on domestic breeding resources. Further restrictions on monkey supply may warrant expansion of existing breeder colonies and establishing additional colonies to assure critical primate needs.

The timed-pregnant rhesus monkey breeding colony stabilized at approximately 260 animals of which 140 animals cycle regularly. The balance represents males, new breeders, and breeders received from contract sources that are available for recycling through contract breeding or intramural research. This colony was supplemented with a research contract which supplied 72 timed pregnant rhesus monkeys to complement the intramural colony production of 80 timed pregnant monkeys. A total of 152 timed pregnant animal models were supplied for intramural research use. A new 3-year contract is being implemented to provide up to 100 timed pregnant rhesus monkeys per year. In addition, three contracts were awarded during the year for timed pregnant baboons. Two of these contracts are fixed fee contracts in which the Government purchases the use of the timed pregnant baboons for intramural research and owns the fetuses and products of conception. The third contract established an NIH-owned colony of breeder baboons at the contractor's site and reimburses the contractor's costs for establishing a monthly supply of timed pregnant baboons for intramural research programs.

#### 4. Research Animal Procurement and Conditioning

##### a. Rodents and Rabbits

The total purchase of rodents and rabbits from contractors further decreased from 132,500 in FY 1973 to approximately 70,000 this year. There was a decline in the use of noninbred mice, rats, and hamsters from contract sources, but a twofold increase in the use of contract rabbits. An itemized list of animals purchased on contract is as follows:

Rabbits--Dutchland	6,200
Sprague Dawley Rats--Taconic	27,000
Hamsters--Lakeview	6,500
Swiss Mice--Taconic	25,000
Rats--Charles River	2,500

In addition, VRB arranged for the Frederick Cancer Research Center to supply NIH investigators about 2,000 Hartley guinea pigs and over 6,000 inbred and nude mice. Arrangements are being made to initiate a Hartley guinea pig contract in which VRB will supply the breeding stock.

##### b. Large Animals

Requests for random source cats were 800 to 850 for FY 1975.

Approximately 484 ungulate animals were purchased, quarantined, conditioned and issued during FY 1975. In addition, some 50 domestic fowl, including ducks, chickens, and turkeys were utilized.



Rhesus (Macaca mulatta) monkey issues for FY 1975 are estimated at about 4,137 which represents an increase of about 626 over FY 1974.

VRB quarantined, selected, and delivered 1,304 rhesus monkeys to Gulf South Research Institute, Hazleton Laboratories, and Perrine as initial breeding stock for rhesus production colonies.

Other species of monkeys (M. fascicularis, M. arctoides, Erythrocebus patas, Saimiri sciureus, Cercopithecus aethiops, Aotus trivirgatus, and Callithrix sp.), contributed small numbers to the overall quarantine and conditioning program.

#### 5. Tissue Culture and Media Production

Based on the first 8 months of FY 1975, the number of requisitions processed for tissue culture and media will total 14,000; a 7 percent increase over last year. The volume of media produced will be 70,000 liters of bacteriologic media and 69,000 liters of tissue culture media for a total of 139,000 liters. This total represents an 8 percent increase over last fiscal year, and reflects for the first time in years an increase of bacteriologic media over tissue culture media.

Issues of blood agar plates of all types, including horse, sheep, and human blood plates will total 159,000 this year, a 7 percent increase.

In addition to blood agar plates, there will be another 406,000 plates of other types for a total of 565,000 plates for the fiscal year. This is a 7 percent increase over last year.

Issues of tissue culture cells as cell suspension will show a slight decrease of 3 percent with a projected total of 200 liters of suspension produced.

Tissue culture cell freezing and storage services continued to be a popular service with NIH investigators. A projected total of over 1800 ampoules of cells will be frozen this year and 2000 ampoules of cells maintained in the frozen cell bank to support research programs requiring this service. This represents a slight decrease over last fiscal year and reflects a tendency of the investigators to use their own storage facilities because of the convenience.

Renovations to provide filtered air to the room housing the automatic bottling system for media dispensing are scheduled for completion late in the fiscal year, almost a year after originally planned, due to contractor delays in correcting minor problems in the installation. Adaptation of a cartridge filter system for sterilization of tissue culture media just prior to the dispensing point of the bottling system is under test. The cartridge system is much more compact than the membrane system used for manual filtration and also allows for increased volume of production lots of media. This change, together with the filtered air to provide a cleanroom atmosphere, should extend the capability for sterile media dispensing to tissue culture, as well as bacteriologic media.

After a period of modification and testing an automatic labeling system has been synchronized with the conveyor belt on the bottling machine to make and apply labels to the bottles as they are filled and capped. This method is expected to greatly reduce the time spent in manual application of labels to the bottles.

## 6. Processing Glassware, Animal Cages, and Miscellaneous Items

Glassware issues to the Institutes and Divisions projected through the end of the fiscal year will total about 8,429,000 pieces; a slight increase over last year. A total of 294,000 cages, racks, and associated pieces of equipment will be processed.

In order to provide adequate coverage on the night shift as well as the day shift, an additional employee was trained in the regeneration process required for the large, mixed bed deionizer. This should prevent the occasional call back time required in the past when the water quality dropped in specific resistance during the evening hours and required someone from the day shift to return for regenerating. A Wilbur terminal was installed in the Glassware Unit to enable direct input for the OFM billing reports and correcting errors generated by faulty information appearing on glassware order forms.

A new form for glassware orders and issues was introduced this year. This new form will provide a record of not only glassware issued, but items of glassware ordered, and some indication of how well the Unit is meeting the demand for glassware. The percentage of each item ordered and supplied by size and type of glassware should provide useful data.

A workload measurement study was conducted in the Unit this year with the help of the Management Analysis office, to calculate new average processing times for individual types of glassware. As a result of this study, several workload improvement recommendations were made and are being implemented. As a preliminary step, a large glassware drying unit, which is no longer required, was removed to create space for installation of a proposed conveyor system to be adapted to the M-2 washer. This conveyor system should reduce the manual handling of glassware baskets as they are filled and transported to the machine for washing.

## 7. Animal Biologics Production

Domestic turkeys and ducks were utilized in small numbers to produce normal blood and antisera for specific research projects.

The canine blood donor colony, which consists of 258 dogs, produced 3,500 units (1 unit = 500 ml) of blood.

Biologics production from ungulate animals is about the same as during FY 1974. Projected production includes 1400 liters of ungulate blood for the year. The size of the ungulate herd being maintained for all purposes increased from 550 to 610 during FY 1975.



## 8. Genetic Repository and New Animal Models Program

VRB rodent colonies were designated as a World Health Organization collaborating center in recognition of the importance of this collection of animal models for biomedical research. The one other collaborating center designated was the Laboratory Animal Center of the Medical Research Council of Great Britain. The director of that center served as a consultant to VRB during a WHO sponsored visit this year.

A committee of the National Research Council studied the VRB small animal program. It concluded that the repository effort should be separately financed through management funding and not supported by inflating the price for animals. About \$500,000 was determined to be the annual cost for maintaining the repository.

A Catalogue of NIH Rodents was published and distributed to about 257 NIH investigators and 765 researchers and specialists in animal science worldwide. It describes characteristics of the over 100 strains and stocks of rodents and rabbits maintained. In addition to supplying animals for intramural investigators, breeding nuclei from these colonies serve as a resource for the international biomedical research community as many of the stocks, strains, and substrains are not available elsewhere. Over 300 investigators were provided with litters of inbred animals to start colonies. This is a twofold increase over FY 1974. Also, several hundred noninbred animals were provided as breeding stock. Several commercial producers were also provided with breeding stock. Requests were particularly numerous for the rat with diabetes insipidus and hypertension, inbred NZB and NZW mouse strains, and inbred guinea pigs.

A program to assist investigators in obtaining new animal models to meet previously unfilled research needs continued. In some instances, new strains of existing laboratory animals exhibiting unique physiological or anatomic characteristics were used. In others, animals having characteristics required in a particular research problem were adapted from nature. New models are hysterectomy derived and foster nursed or hand nursed prior to introduction into the NIH colonies. Twelve new strains were added to the repository at the request of NIH investigators. They are:

<u>Mice</u>	<u>Rats</u>	<u>European Giant Hamster</u>
BALB/cCRN	WFU/CrN	<u>Guinea Pig</u>
A. 0AKR	SHRSP/A1N	
Dwarf (dw)	SHRSP/A3N	PCA (passive cutaneous anaphylaxis)
Motheaten (me)	Corpulent (cp)	
Dystrophic-2 (dy-2)		
BDL-ky (kyphoscoliosis)		

## 9. Experimental Surgery, X-ray, and Related Activities

### a. Building 14E and 28 Facilities

The surgical facilities are primarily available to B/I/RD investigators; however, surgery was frequently performed by staff veterinarians assigned to

the Section at the specific request of investigators. Assistance to investigators was provided in anesthesiology, surgical support, diagnostic radiology and postoperative care of animals.

The number of surgical procedures stabilized at approximately 800 per year and the facilities were used at maximum capacity. An increase of 10 percent is projected next year since the Surgery Unit relocated from Building 28 to 14E and will provide more surgical space. The Surgery Unit maintains a 500-milli-ampere radiographic unit with fluoroscopy which adds an improved service for research and clinical support to laboratory animal medicine.

#### b. Animal Center Ungulate Surgery

Activities in ungulate surgery declined. Projects utilizing sheep for intrauterine fetal surgery have ceased. Surgery was utilized for porcine skin transplantation procedures, collection of fetal pig serum, and to treat a variety of clinical conditions. Miniature swine breeding is continuing to develop four inbred lines of immunologically distinct animals. Five sows produced progeny this year.

Radiographic procedures increased from 250 exposures in FY 1974 to 420.

### 10. Experimental Animal Holding

#### a. Primates

Renovations for Phases II and III of Building 14D will be awarded to contractors before the end of FY 1975, and estimated completion date is 12 months after the award date. This renovation is a joint program between DRS and BoB which will provide a centralized research primate holding facility. The new renovations are designed to permit infectious disease studies, provide a safe working environment for personnel, and minimize cross-infection among primates. The total capacity of the facility, including the conventional primate facilities of Phase I renovations, will establish one of the largest primate research facilities in the country with a maximum primate population of over 1900 animals.

#### b. Large Laboratory Animals

The research holding facilities of Building 28 has increased its scope of research support by greater diversity of animal species including: dogs, cats, miniature swine, goats, sheep, and other large laboratory animals. In addition, new collaborative DRS research programs with NCI and NHLI were initiated. Continued use of a contract to hold dogs off the Bethesda campus allowed improved utilization of space for studies requiring constant investigator attention. The atherogenic diet study in dogs in Building 14E will relocate to Building 28.

The population of research animals in this facility averages approximately 360 per month. Additional research animals, requiring only infrequent investigator manipulation, are maintained on contract. This has permitted a more suitable animal density population per kennel to achieve better animal care

management. Recent renovations of two large animal wards in Building 28 significantly improved animal welfare, and improved the research environment and employee working conditions.

## 11. Animal Nutrition

VRB-developed, open formula rations continue to be used throughout the NIH. Purchase arrangements were made through competitive contracts for three new open formula rations; autoclavable rations for rats and mice, rabbits and guinea pigs. Based on current prices, the open formula rations purchased under competitive contracts cost 36 percent less than the closed formula rations purchased under noncompetitive contracts. When this price differential is applied to the open formula feeds purchased under competitive instead of noncompetitive contracts, an apparent savings of approximately \$115,000 will be realized by NIH during the contract year.

The NIH, open formula ration for conventionally reared rats and mice was adopted as a standard reference ration by committees of the American Institute of Nutrition and the National Research Council.

The proximate nutrient, calcium, and phosphorous concentrations in NIH contract animal feeds were monitored. This information is useful in demonstrating to investigators the variation in nutrient concentrations among production batches of a given ration.

The contract to conduct nutrient analyses on experimental rations was expanded to include assays for various feed contaminants. At least one sample collected from all animal feeds purchased under NIH contracts has been assayed for heavy metals and pesticide residues. To date, the concentrations of these potential contaminants have been either undetectable or within acceptable ranges.

An open formula, autoclavable ration containing 18 percent crude protein is being fed to SPF production colonies of rats and mice on a trial basis. There has been no apparent decrease in the reproductive performance of animals fed this ration as compared to animals fed a commercial ration containing 24 percent crude protein. Similar results were obtained under experimental conditions.

## 12. Animal Health

### a. VRB Animal Health Problems

A pinworm eradication program was initiated in conventional mouse production colonies. Piperazine was proportioned into the drinking water continuously for a one-month period while the buildings were being disinfected with an iodophor to destroy pinworm ova. Following this, treatment was alternated every other week and untreated, helminth-free sentinal animals placed in the rooms were monitored to determine whether total eradication was achieved. Plans were made to use dichlorvos to treat a mite infestation discovered in inbred mouse production colonies.

An outbreak of Tyzzer's disease occurred in C-wing rabbits early in the year. Tylosin in the drinking water was found to be therapeutically effective, stopping the outbreak after only 20 deaths. A major epizootic may have been averted since the C-wing rabbits have been free of the disease and are probably highly susceptible. Inasmuch as the causative agent is a spore former, it is considered likely that it will gain entrance into the colony again. The indirect fluorescent antibody technique has been used in preliminary studies of the natural history of the disease and to demonstrate antigenic similarities between the causative agent in rabbits and the agent recently isolated from horses. Because of shortcomings of this method for serologic survey work, several antigens are being tested in the development of a complement fixation test. As more is learned about the antigens, hopefully, the preparation of a vaccine will become possible.

Although Tylosin was effective in treating C-wing rabbits for Tyzzer's disease, its use appeared to precipitate a severe outbreak of enterococcolitis which resulted in 108 deaths in one month. Enterococcolitis has been present in C-wing rabbits for several years, causing an average of about 20 deaths per month. Culture results have indicated that it is caused by imbalances of intestinal microflora, particularly overgrowth of E. coli, which may be stimulated by the use of certain antibiotics such as Tylosin. It is postulated that these cesarian-derived rabbits are "too clean" and that additional bacteria are needed to broaden the intestinal microflora to provide effective competition for E. coli. For this reason, attempts were made to acquire specific pathogen-free rabbits from other sources to act as microfloral donors. Two attempts failed. The rabbits from one source had coccidiosis and those from another source were infected with Bordetella bronchiseptica.

The barrier-maintained mouse colony suffered its worst recorded outbreak of hemothorax. The outbreak lasted 2 months. All strains of mice were affected, and virtually all males over the age of 6 months were lost. As previously described, this disease appears to be a noninfectious condition of male mice characterized by myocarditis and prolonged clotting time. The cause of the sporadic outbreaks is not known. It has been postulated that some noxious substance, which secondarily increases the mouse's requirement of vitamin K, periodically finds its way into the ration. Supplemental vitamin K was added to the diet of the barrier mice but, unfortunately, this was at about the time the outbreak was subsiding so that the effect was impossible to evaluate. A beneficial effect was suggested, however, by the finding that only a few scattered hemothorax fatalities occurred in the 9 months since the supplemental vitamin K was started. The results of a recent pilot study indicate that the disease can be reproduced by feeding mice excessive vitamin A, which is known to increase the mouse and rat requirements for vitamin K.

The incidence of Johne's disease in goats increased. Fecal culturing for Mycobacterium paratuberculosis in the goat herd was continued during FY 1975. The incidence of Johne's disease declined from 21 cases in 1972 to two in 1973 and rose to five in 1974. Culturing will be continued indefinitely on a semi-annual basis. The disease is considered difficult to eradicate since the causative organism is relatively stable in the environment and its detection in animals incubating the disease is laborious. Goats may incubate the disease for several years before fecal cultures reveal the causative agent. Current



information indicates that Johne's disease is endemic in Maryland and that anyone buying goats on the open market will, in time, purchase animals with the disease.

The monkey breeding facility at Perrine, Florida, experienced an outbreak of progressive debilitating disease characterized by alopecia, acneform dermatitis, facial edema, squamous metaplasia in palpebral glands, hypertrophic gastritis and death. Many of the clinical and histopathologic findings are compatible with hypovitaminosis A which, in rhesus monkeys receiving adequate amounts of dietary vitamin A, points to the possibility of toxic exposure to chlorinated hydrocarbons. Preliminary chromatographic analysis of tissue specimens from affected monkeys indicates that the toxic substance may be polychlorinated biphenyls (PCB's). PCB's are known to be rapidly toxic for rhesus monkeys in very low dose, 2 ppm in feed, and to produce similar lesions to those occurring in the Perrine monkeys.

Brucellosis testing is now performed annually in the swine and goat herds and in the sheep flock. All new acquisitions are tested during the quarantine period. No new cases were observed.

Urolithiasis was diagnosed in 12 goats (wethers) and six sheep (wethers). Three of the cases were fatal. The disease is thought to be associated with the exclusive feeding of grain concentrates, and may also be related to mycoplasma infections.

#### b. B/I/D Animal Health Problems

No large-scale epizootics such as mouse pox occurred in the B/I/D's this year. Examples of lesser problems included the occurrence of cervical lymphadenopathy in rats purchased on contract from a VRB contractor. The rats showed facial edema and failed to sustain Walker carcinomas. Autopsies on animals on the day of arrival in the laboratory revealed tracheitis and pronounced peritracheal lymphadenopathy. Pasteurella pneumotropica was isolated from the lymph nodes in six of eight animals cultured. The commercial colony was found to be serologically positive for Sendai virus, which is reported to augment the pathogenicity of P. pneumotropica infections. The company that produced the rats was required to correct the problem.

Assistance was extended to the B/I/D's also in the form of participation in collaborative research of several types, including hepatitis A & B transmission studies and studies of the effects of thymus- and bone marrow-derived lymphocytes on the pathogenesis of autoimmune disease in NZB mice.

#### 13. Animal Disease Investigation Service

The Animal Disease Investigation Service answered 182 calls for assistance from the B/I/D's, or approximately the same number as last year. These involved consultative, diagnostic, and therapeutic activities. Animal species encountered were varied; including rodents, rabbits, primates, carnivores, and miscellaneous feral animals. The complexity of the calls also varied and involved all Institutes. Ninety-four of the investigations required supplemental pathology exams, 38 required microbiologic testing and 30 utilized



clinical pathology tests. This service has been extremely well received by B/I/D investigators. The service continues to be mutually beneficial to investigators and to the VRB professional staff.

#### D. Problems

Problems of animal disease are referred to in Part II, C, 12, a and b.

It now appears that the program initiated in 1968 to hysterectomy derive foundation colonies for all mouse and rat strains and stocks may not result, as expected, in the issuance of strictly pathogen-free animals to investigators. Although VRB barrier colonies remain uncontaminated for periods beyond expectation, the production colonies in conventional facilities were reinfested with internal and external parasites. Whether this was due to inadequate decontamination of facilities or a recontamination by a flourishing resident feral rodent population in the Building 14-28 complex is undetermined. Perhaps the design, construction, location, state of repair, and age of the buildings housing the present rodent colonies make it unrealistic to expect maintenance of a totally pathogen-free status of rodents following hysterectomy derivation. The facilities for rodent production are not barriers and are in close proximity to quarters for primates, sheep, and carnivores. Nonetheless, the effort to produce pathogen-free rodents will continue.

Some General Schedule (GS) Biological Laboratory Technicians working in the barrier are being paid less than some Wage Grade (WG) animal caretakers in conventional colonies performing less technically skilled work. The conversion of these employees to GS pay scale has worked to their disadvantage because of large WG pay increases. General Schedule technicians in the gnotobiotics unit and professional services staff, as well as the barrier, are inadequately compensated compared to WG employees. Unless the situation is corrected, recruitment of qualified employees into these areas will become impossible. Employees presently assigned these jobs are becoming interested in leaving or returning to WG animal caretaker positions.

#### E. Program Plans

Consideration will be given to requesting approval to establish a committee to advise VRB whether strains warrant being added to or dropped from the genetic repository, as recommended by the NRC committee reviewing NIH rodent activities.

A computerized record keeping system is being developed by VRB personnel and the DRS management analysts. Primary emphasis is on collection of data on rodent breeding performance. Mating and mortality data will also be collected.

An expanded program of genetic monitoring is necessary to provide adequate safeguards for the integrity of inbred strains. A routine testing program involving test matings, histocompatibility testing, and mandible analysis will be established.

Present obsolete cages for rabbits and guinea pigs will be replaced as soon as funding is available and an acceptable design tested. The evaluation of

a semiautomated cage for rabbits continues and plastic cages for guinea pig harems are being tested.

The disease surveillance program for the rodent colonies must be enhanced to ensure prompt detection of disease through VRB monitoring. The effort to free all rodent strains and stocks of disease through hysterectomy derivation will continue. Methods will be developed for applying this practice to guinea pigs and rabbits. This requires a cooperative effort in areas of nutrition, microbiology, and genetics.

An effort will be made to survey requirements of investigators for rodents beyond the capability of in-house production and to initiate new contracts to meet these needs where possible, using VRB colonies as the genetic base.

Studies to define the major nutrient requirements of different species and strains of inbred rodents will continue. Efforts will continue to develop open formula rations purchasable through advertised contracts to replace closed formula rations purchased through negotiated, sole source contracts.

It is expected that the Carnivore Unit will be reorganized before the end of FY 1975; canine long-term holding will replace random source dog activities. A canine socialization program was initiated and will be developed for continuing application to colony reared dogs. Continued expansion of the canine breeding colony by purchase of quality dogs from outside sources will be pursued. Contract production of purebred foxhound puppies (approximately 500/year) will be continued into and beyond FY 1976. Plans are being developed to create outdoor housing space for growing puppies. This program will permit purebred production to expand by 200-300 per year.

The dairy goat and burro breeding herds will be expanded during FY 1976. About 15 jennies will be bred in FY 1975 and are expected to foal in the spring of FY 1976.

Health surveillance of ungulate herds and flocks will be expanded and intensified during FY 1976. Emphasis will be placed on identification and containment of equine diseases because of implementation of a burro breeding program.

Further definition of the blood groups of dogs in the canine donor and breeding colonies will be undertaken when "typing" anitsera becomes available from outside sources.

Contract primate breeders will have been supplied all necessary breeding stock before the end of FY 1975. Thereafter, efforts will be directed toward supplying the contractors with replacement rhesus breeding stock on a continuing basis. Animal Center programs will be readjusted in order to provide holding space for young monkeys produced by contractors.

Improvement of leased property, consisting of some 200 acres of pasture and several buildings adjacent to the Animal Center will provide space for programs utilizing sheep, swine, and burros. Partial improvement of a pole barn and installation of fences enclosing about 40 acres will permit expansion

of sheep activities (100-200 head) early in FY 1976. Expansion of swine breeding/holding activities is anticipated late in FY 1976 with the erection of a temporary farrowing/holding structure.

Within the limits of current manpower restrictions and space limitations, continued efforts will be made to expand or improve automation of media production. Continually increasing demands for bacteriologic media in plates require the development or purchase of improved automated equipment for this area of production. Quality control procedures will be expanded to focus more emphasis on those aspects of bacteriologic media production which can be monitored with limited space and personnel.

The possibility of using automatic data processing methods for inventory and ordering of supplies will be explored. The shortages of various items of supply make more efficient inventory and ordering methods mandatory if production slowdowns are to be avoided.

A survey is being conducted by PEB to determine costs associated with the current methods for regeneration of the large mixed bed deionizers. Items monitored will include water usage per day, cost of caustic soda and hydrochloric acid for regeneration, and labor costs. Consideration will be given to the possibility of contracting for this service, automating the present equipment, or continuing the present manual system of regeneration.

The possibility of replacing the outdated cage and rack washers in the Clinical Center cagewashing unit is being explored. The proposed consolidation of the NCI animal rooms in the B corridor adjacent to the cagewashing unit is expected to increase the workload on existing equipment and personnel. Purchase of new equipment is recommended as the expense of upgrading existing equipment, due to its age, is uneconomic.

#### F. Publications

Bacher, J.D. and Potkay, S.: Intussusception of the Small Intestine (ileum): What is your diagnosis? J. Amer. Med. Assoc., 164: 1135-1136, 1974.

Ganaway, J.R.: Bacterial, mycoplasma, rickettsial disease. In Wagner, J. and Manning, P. (ed.): Biology of the Guinea Pig. New York, N.Y., Academic Press, in press.

Ganaway, J.R.: Bacterial Zoonoses of Laboratory Animals. In Melby, E.C., Jr. and Altman, N.H. (ed.): CRC Handbook of Laboratory Animal Science, Vol. II. Cleveland, O., CRC Press, 1974, pp. 243-257.

Potkay, S., Bacher, J.D., and Pitts, T.W.: Feline Infectious Peritonitis in a Closed Breeding Colony. Lab. Anim. Sci., 24: 279-289, 1974.

Potkay, S. and Bacher, J.D.: The Research Dog: Random Source or Colony Bred? In Harmison, L.T. (ed.) Research Animals in Medicine. DHEW Publication No. (NIH) 72-333, 1973, pp. 1061-1065.

Scott, R.N., Faraci, R.P., Goodman, D.G., Militano, T.C., Gaelhoed, G.W., and Chretien, P.B.: The role of inflammation in bronchial stump healing. Ann. Surg. in press.

Strandberg, J.D., and Goodman, D.G.: Animal Model: Canine Mammary Neoplasia. Am. J. Pathol., 75: 225-228, 1974.

Whitney, R.A., Jr.: A Domestic Primate Production Feasibility Study. In Bermant, G. and Lindburg, D.G. (ed.): Primate Utilization and Conservation. John Wiley, & Sons, Inc., 1975, pp. 163-167.





### III. INDIVIDUAL PROJECT REPORTS

Serial No. Z01 RS 00001-05 VR  
1. Veterinary Resources Branch  
2. Small Animal Section  
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

#### C. GENETIC ANALYSIS AND ANIMAL MODEL DEVELOPMENT

D. DRS-VRB-3

E. C.T. Hansen

F. K.P. Smith

G. Laboratory of Bacterial Products, BoB  
Laboratory of Immunology, NIAID  
Laboratory of Pathology, GLC, NCI

H. Total: 1.0  
Professional: 0.5  
Others: 0.5

I. Objectives: 1) To study the role of genetic and environmental components involved in the dynamics of reproductive performance of inbred strains of animals, 2) genetic monitoring of inbred strains, and 3) develop new animal models utilizing the existing gene pool and new and exotic species.

Methods Employed: Comparison of tumor frequencies between conventional and SPF inbred strains suggests for the most part that establishing these animals in an SPF environment does not affect either the age of onset or frequency. One exception has been in the C3H/HeN strain in which the appearance of mammary tumors occurs at a somewhat earlier age and the growth of the tumor is more rapid.

The genetic analysis of blood pressure continues. Measurements in the 19 inbred strains of rats show almost a normal distribution of blood pressures suggesting a complex form of inheritance. Blood pressure measurements in progeny of crosses of a selected number of these rat strains is now underway. A series of diallel crosses between a number of these strains show a marked sex difference in the pattern of inheritance. In female progeny, the evidence suggests an additive form of inheritance whereas in males, the inheritance appears to be nonadditive.

Selected breeding for the sensitivity and resistance to the effect of histamine after treatment with B. pertussis has reached the eighteenth

generation. Sensitivity has increased to 85 percent in the sensitive strains and decreased to 3-5 percent in the resistant strain from an average sensitivity of 30 percent in the unselected base population.

A program has been undertaken to develop a mating system for the maintenance of outbred SPF nucleus colonies of mice and rats. The goal of this program is to develop a system which meets the requirements for maintaining a stable gene frequency, minimize inbreeding and reduce the requirement for close professional supervision. Several revisions have been made during the course of this program and the present technique appears to be successful in meeting the majority of the requirements.

A long-term study with the nude (athymic) mouse continues. This animal is very unique in that the thymus fails to develop with the result that half of the immune mechanism is absent. The potential of this animal for immunological and cancer research is considerable. The project consists of two phases. First, to develop techniques and procedures for large-scale production since it is extremely susceptible to various infections. Second, to establish this gene on a number of inbred strains to study the effect that the absence of the thymus mediated immune system has on established immune responses and tumor frequencies of these inbred strains. A program has been undertaken to backcross the nude gene into 19 inbred mouse strains. Two of these 19 strains have reached a minimal level of identity and can now be used for research purposes.

Significance: The significance of these projects is to develop, by the use of genetic procedures, new animal models which have an application to biomedical research.

- J. Genetics; genetics, population genetics, inbreeding; mammals, mice; mammals, rats.
- K. Continuation
- L. None

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

C. DEVELOPMENT OF DIETS FOR LABORATORY ANIMALS

D. DRS-VRB-4

E. J. J. Knapka

F. F. J. Judge  
K. P. Smith

G. None

H. Total: 2.0  
Professional: 0.5  
Others: 1.5

I. Objectives: 1) To formulate and evaluate open formula rations designed to improve the nutritional status of laboratory animal colonies, and 2) to accumulate data regarding the specific nutrient requirements of various strains of inbred laboratory rodents.

Methods Employed: A series of factorial-designed feeding trials are conducted to determine the effect of various diets differing in nutrient concentrations and physical form on the growth and reproductive performance of the species involved. Criteria of evaluation include number of pregnancies, number of offspring weaned, weight of offspring weaned, and the post-weaning growth rate of offspring. These data are coded for computer analysis by the appropriate statistical methods.

Major Findings: Mouse reproduction data collected under practical conditions verify experimental data indicating no decrease in reproductive performance when dietary concentrations of crude protein is decreased from 24 to 18 percent.

Data collected from a study designed to evaluate the effect of high concentrations of thiamin in autoclavable mouse rations indicate the concentrations of thiamin fortifications used in commercial rations are considerably in excess of requirements. These data also indicate there are no antimetabolites produced that affect mouse reproduction during autoclaving of feeds containing high concentrations of thiamin.

The concentrations of ascorbic acid required in autoclavable guinea pig rations have been established. Limited data have been accumulated that indicate metastatic calcifications in guinea pigs can be controlled by altering dietary mineral concentrations.

Significance: The development of open formula rations for NIH production and research animal colonies is advantageous because 1) production of rations is not restricted to a single mill in the event of a fire or bacterial contamination, 2) investigators have the opportunity to know the complete nutritional status of animal colonies, 3) a basis is provided for the improvement of rations for particular stocks or strains of animals, and 4) competitive procurement of essentially the same product can be accomplished over many years.

The efficiency of maintaining production and research colonies of laboratory animals can be markedly improved if rations can be developed that supply nutrients in concentrations nearly equal to the requirement of the strain of animal involved.

Proposed Course: Continuation

J. Models, biological; nutrition, diet; growth; reproduction; food, animal feeds.

K. None

L. Knapka, J.J. and Judge, F.J.: The Effects of Various Levels of Dietary Fat and Apple Supplementation on Growth of Golden Hamsters (Mesocricetus auratus). Lab. Anim. Sci. 24: 318-325, 1974.

Knapka, J.J., Smith, K.P., and Judge, F.J.: Effects of Open and Closed Formula Ration on the Performance of BALB/cAnN, C57BL/6N, and Swiss Mice. Lab. Anim. Sci. 24: 480-487, 1974.

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

C. SELECTION FOR 6-WEEK WEIGHT IN INBRED AND NONINBRED STRAINS OF MICE

D. DRS-VRB-7

E. K. P. Smith

F. C. T. Hansen

G. None

H. Total: 1.0  
Professional: 0.5  
Others: 0.5

I. Objectives: To determine if a significant amount of genetic variation still exists within highly inbred strains of mice.

Methods Employed: The design includes three strains of mice--two inbred ( $C3H^+$ /HeN and NGP) and one noninbred (GP). There are 72 mating pairs per strain. In each strain there are three groups: 1) 12 pair of brother x sister matings, 2) 24 pair of random matings, 3) 36 pair of random matings which are selected for 6-week body weight. The experiment will include six generations.

Major Findings: After four generations, there was no response to selection for 6-week body weight in the  $C3H^+$ /HeN strain. This result indicates there is no remaining genetic variation in the  $C3H^+$ /HeN strain and it was discontinued after the fourth generation. After five generations of selection in the GP strain, there has been a large response to selection. There is a 5 gm. difference between the GP control line and the GP selected line. These results indicate that 38 percent of the variation observed in 6-week weight is due to genetic differences.

Significance: If it can be demonstrated experimentally that all of the genetic variation in a quantitative trait such as 6-week body weight has been eliminated from highly inbred strains, it should be possible to simplify the mating systems used and reduce production costs.

Proposed Course: Continuation



J. Genetics, population genetics animal; genetics study section; body weight; mammals, mice Swiss; mammals, mice C3H/HeN; genetics, population genetics, inbreeding.

K. None

L. None

Serial No. ZOI RS 00004-14 VR  
1. Veterinary Resources Branch  
2. Comparative Pathology Section  
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

- C. TYZZER'S DISEASE
- D. DRS-VRB-5
- E. James R. Ganaway
- F. Rebekah S. McReynolds  
Anton M. Allen  
Thomas D. Moore
- G. University of Kentucky (Dr. T.W. Swerczek)
- H. Total: 1.7  
Professional: 1.0  
Others: 0.7
- I. Objectives: To characterize the etiologic agent. To study the pathogenesis of the disease through experimental transmission studies. To develop serologic techniques for detection of antibody. To develop a means to control and/or prevent the disease.

Methods Employed: Microbiology, immunology and pathology.

Major Findings: The disease continues to occur enzootically in the NIH rabbit production colony. Biological characterization and comparison of isolants from laboratory rabbits and a foal which died of Tyzzer's disease continues. Several antigen preparations have been tested in the development of a complement fixation test.

Significance: Within the past decade, this disease has been diagnosed for the first time in nine different species of animals including rats, hamsters, gerbils, rabbits, cats, muskrats, wild hares, nonhuman primates, and horses. The natural history of this disease remains unknown. The etiologic agent, a gram-negative, spore-forming, obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. This disease occurs throughout the world, causes fatal epizootics in a wide variety of species, and is one of the most important diseases of laboratory animals which interferes with and complicates biomedical research.

Proposed Course: Continuation

J. Bacterial diseases; liver disorders, hepatitis; gastrointestinal disorders, enteritis, colitis; mammals, lagomorphs.

K. None

L. None

Serial No. Z01 RS 00005-01 VR  
1. Veterinary Resources Branch  
2. Comparative Pathology Section  
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

- C. SUPPRESSION OF PSEUDOLYMPHOMA IN NZB MICE WITH SYNGENIC YOUNG THYMOCYTES
- D. None
- E. Dawn G. Goodman
- F. M. Eric Gershwin, NIAMD  
Alfred D. Steinberg, NIAMD  
Robert A. Squire, NCI
- G. Arthritis and Rheumatism Branch, NIAMD  
Carcinogenesis, Division of Cancer Cause and Prevention, NCI
- H. Total: 0.5  
Professional: 0.25  
Others: 0.25

- I. Objectives: To determine the effect of restoration of immune competent cells with and without immunosuppression on the development of pseudo-lymphomatous infiltrates in NZB mice.

Methods Employed: NZB mice are used. Mice are treated with young thymocytes, young spleen cells, young bone marrow cells, a combination of all three types of cells, or with old spleen cells on a regular schedule. These groups are subdivided with one group also receiving Imuran. In addition, two control groups, one with no treatment and one treated only with Imuran are used.

At the end of a year, the mice are sacrificed and autopsies performed on animals. The various lesions present will be evaluated histologically and correlated where possible with treatment group.

Major Findings: Currently unknown.

Significance: Elucidation of some thymocyte functions with possible implications in control of neoplastic diseases is hoped for.

Proposed Course: Continuation

- J. Mammals, mice NZB; blood cells, B lymphocytes; blood cells, T lymphocytes.
- K. None
- L. None

Serial No. Z01 RS 00006-03 VR  
1. Veterinary Resources Branch  
2. Small Animal Section  
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

C. DIFFERENT LEVELS OF DIETARY PROTEIN FOR LABORATORY RATS

D. DRS-VRB-2

E. Anton M. Allen  
Joseph J. Knapka

F. K.P. Smith

G. None

H. Total: 0.5  
Professional: 0.25  
Others: 0.25

I. Objectives: To evaluate the effect of various levels of dietary crude protein on the reproductive performance, various physiological systems, pathology, and longevity of nonbred stocks of rats.

Methods Employed: A series of factorial designed, long-term feeding trials are conducted involving rations containing various concentrations of crude protein. Throughout the study various reproductive trials and physiological determinations are recorded. At predetermined intervals, rats from each treatment group are sacrificed for pathological evaluation.

Major Findings: Analyses of pathology data have not been completed.

Proposed Course: Continuation

J. Proteins; nutrition; mammals, rats.

K. None

L. None



PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

C. ENVIRONMENTAL TOXICOSIS OF RHESUS MONKEYS--PERRINE PRIMATE FACILITY

D. None

E. George L. Clarke

F. Anton M. Allen  
Albert E. New  
Norman Altman

G. Perrine Primate Research Center

H. Total: 0.5  
Professional: 0.4  
Others: 0.1

I. Objectives: To determine the cause of progressive debilitation and death among the rhesus monkeys housed at the Perrine, Florida, facility.

Methods Employed: The problem is being studied by histopathological, clinical, pathological, and epidemiological means. The history and pathology is suggestive of a toxicosis produced by exposure to polychlorinated biphenyls (PCB). Tissues and materials suspected of containing these compounds are being analyzed by gas chromatographic and mass spectrophotometer methods.

Major Findings: Preliminary investigations indicate the presence of PCB's in tissues of affected animals.

Proposed Course: Continuation

J. Toxicology; halobenzenes, PCB and PCT; mammals, primates.

K. None

L. None

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

C. NEOPLASIA IN THE NUDE MOUSE

D. None

E. George L. Clarke

F. Carl T. Hansen

G. Carcinogenesis Branch, NCI

H. Total: 0.3  
Professional: 0.2  
Others: 0.1

I. Objectives: To determine the prevalence and types of neoplasia that occur in this inbred strain which is genetically deficient in cell mediated immunity.

Methods Employed: Retired females are maintained behind the barrier at Building 14C for aging and sent to the Comparative Pathology Section when they show any signs of abnormality. Males are sent to the Section following retirement and are maintained in relative isolation in the Horsfall units and killed when they exhibit any abnormal signs.

Major Findings: There are sketchy reports that claim nude mice have a relatively low rate of neoplasia. Numerous cases involving neoplastic changes have been observed to date, involving many organ systems.

Significance: If nude mice in fact do experience a significant rate of neoplastic disease, this will be a worthwhile contribution to the scientific literature.

Proposed Course: Continuation

J. Mammals, mice; neoplasms; immunopathology, immunologic deficiency disorders.

K. None

L. None

1. Veterinary Resources Branch
2. Experimental Surgery and  
Medicine Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1974 through June 30, 1975

C. SODIUM CYANATE NEUROTOXICITY IN Macaca nemestrina primates

D. DRS-VRB-8

E. David K. Johnson

F. Robert A. Whitney, Jr.  
French Anderson, NHLI

G. Section on Molecular Hematology, NHLI

H. Total: 0.6  
Professional: 0.3  
Other: 0.3

I. Objectives: Sodium cyanate, a chemotherapeutic agent for Sickle Cell disease, inhibits irreversibility of the sickling of erythrocytes from patients with this disease by reacting specifically with the NH<sub>2</sub>-terminal valine of the hemoglobin molecule without significantly destroying erythrocyte metabolism or function. It has been suggested that sodium cyanate may elicit neuropathology in pigtail monkeys, Macaca nemestrina. The outcome of this study will provide information for development of further clinical studies for use in humans suffering from Sickle Cell disease.

Methods Employed: Twenty adult female pigtail monkeys, Macaca nemestrina, will be divided into four groups; one as a sham control and the other three groups will receive daily subcutaneous injections of sodium cyanate at 40, mg/kg; 25 mg/kg; and 15 mg/kg, respectively. Selected animals will be humanely killed and perfused for neuropathological examination. Clinical neurological examination and clinical laboratory tests will be run routinely during the course of the experiment. Baseline hematology, clinical chemistries, and neurological evaluations have been compiled over 3-month stabilization period.

Proposed Course: Initiate the sodium cyanate testing experimental protocol in one month.

J. Hemoproteins, hemoglobinopathies, sickle cell anemia; cyanates; mammals, primates; models, biological; neurotoxins.

K. None

L. None

1. Veterinary Resources Branch
2. Experimental Surgery and  
Medicine Section
3. Bethesda

PHS-NIH

Individual Project Report

July 1, 1974 through June 30, 1975

C. Erythrocebus patas MONKEY AS AN ANIMAL MODEL FOR  
CARDIOVASCULAR RESEARCH

D. DRS-VRB-9

E. David K. Johnson

F. Donald L. Fry, NHLI  
Robert Mahley, NHLI

G. Section on Experimental Atherosclerosis, ODIR, NHLI

H. Total: 3.0  
Professional: 0.75  
Other: 2.25

I. Objectives: 1) To determine the suitability of the patas monkey for atherosclerotic studies as they relate to human disease. Positive findings would provide an animal model from an African source, and 2) to determine whether the patas monkey has advantages as an animal model for cardiovascular studies over those presently available.

Methods Employed: Fifty patas monkeys (Erythrocebus patas) were purchased and maintained on monkey chow for 4 months while baseline data was obtained. They were randomly divided with equal sex distribution into one group of 10 animals receiving monkey chow, one group of 20 receiving high fat-low cholesterol, and one group of 20 receiving high fat-high cholesterol. Monthly blood samples were drawn and hematological, serum chemistries, and serum lipid profiles were obtained.

Major Findings: The test group receiving high fat-high cholesterol had a rise in serum cholesterol levels which persisted while being fed the atherogenic diet. The serum lipid profiles of the other two groups were similar. After 12 months on the study, one-half of each group was humanely killed and necropsies performed with emphasis placed on the cardiovascular system. Atherosclerosis lesions were evident in the high fat-high cholesterol group. After the end of an additional 12 months, the balance of the animals were humanely killed and necropsied. More severe atherosclerosis was evidenced in the high fat-high cholesterol group with evidence of some coronary artery disease and a few cases of cholesterol gallstones. The high fat-low cholesterol animals had some indication of mild disease, and detailed histological and histochemical evaluations are now in progress.

Proposed Course: The patas monkey is a suitable primate animal model for atherosclerosis. Arterial lesions, serum lipids, and serum chemistries have characteristics comparable to human disease. The next study will be to divide 40 patas monkeys into three groups: a test group receiving a diet similar to a typical American diet, another group a diet with added cholesterol, and a control group. This study is proposed for a minimum of 2 years duration with similar parameters followed.

- J. Mammals, primates; models, biological; cardiovascular disorders arteriosclerosis, atherosclerosis; cholestane series, cholesterol; lipids, blood.
- K. None
- L. In preparation

Serial No. Z01 RS 00011-01 VR  
1. Veterinary Resources Branch  
2. Experimental Surgery and  
Medicine Section  
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

- C. EFFECT OF SEASON ON PITUITARY AND GONADAL HORMONE LEVELS IN ADULT MALE MACAQUES
- D. None
- E. David K. Johnson
- F. Gary D. Hodgen
- G. Section on Endocrinology, Reproduction Research Branch, NICHD
- H. Total: 1.25  
Professional: 0.25  
Others: 1.00
- I. Objectives: Season changes in breeding efficiency among colonies of rhesus monkeys remains a controversial issue with little pertinent scientific data available. Effects of season on hormonal parameters important in male fertility gonadal secretions are involved. Measurements of Follicle Stimulating Hormone, Leutining Hormone, Testosterone, and Androstenedione in peripheral serum will be assayed for 5 consecutive days every month in ten adult breeder male monkeys. Correlations between hormone levels, breeding efficiency, and season will be determined.
- J. Mammals, primates; reproductive hormones, gonadotropins; reproductive system, gonads.
- K. None
- L. None



Serial No. Z01 RS 00012-01 VR  
1. Veterinary Resources Branch  
2. Experimental Surgery and  
Medicine Section  
3. Bethesda

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

- C. HORMONE LEVEL DURING THE POSTPARTUM INTERVAL  
IN NURSING AND NON-NURSING MACAQUES
- D. None
- E. David K. Johnson
- F. Gary D. Hodgen
- G. Section on Endocrinology, Reproduction Research Branch, NICHD
- H. Total: 2.0  
Professional: 0.50  
Others: 1.50
- I. Objectives: The interval from delivery to the first fertile menstrual cycle in rhesus monkeys is not known. Breeding management requires such information to maximize the use of breeder males for space management planning and efficiency in timed-mating protocols. Five nursing mothers and five non-nursing mothers will be bled daily for 90 days beginning one day after delivery. Serum levels of Follicle Stimulating Hormone, Luteinizing Hormone, Estradiol, Estrone, and Progesterone will be measured to identify the onset of ovulatory menstrual cycles.
- J. Mammals, primates; reproductive hormones, gonadotropins; reproductive system, gonads.
- K. None
- L. None

Serial No. Z01 00013-01 VR  
1. Veterinary Resources Branch  
2. Animal Center Section  
3. Poolesville

PHS-NIH  
Individual Project Report  
July 1, 1974 through June 30, 1975

C. MYCOPLASMA INDUCED CAPRINE KERATOCONJUNCTIVITIS

D. None

E. Ervin J. Baas  
Michael Barile (BoB)

F. R.M. Franklin

G. Mycoplasma Section, Laboratory of Bacterial Products, BoB  
Wilmar Ophthalmology Institute, The Johns Hopkins University

H. Total: 0.4  
Professional 0.2  
Others: 0.2

I. Objectives: To determine: 1) if Mycoplasma conjunctivae is the etiological agent of natural occurring caprine keratoconjunctivitis (pinkeye) and arthritis, 2) if the disease or similar pathological changes can be induced experimentally, and 3) whether the goat is a suitable animal model for Reiter's Syndrome (irridocyclitis, urethritis, polyarthritis, conjunctivitis) in humans.

Methods Employed: Naturally occurring cases of conjunctivitis and arthritis in goats are being studied by bacteriological, serological, pathological, and serum chemical methods. This information is being utilized to further understand and contribute to the experimental induction and pathogenesis study of the disease. The experimentally induced disease is being studied by the previously mentioned parameters.

Major Findings: Natural epizootics occur in cyclic periods. Subsequent to these periods, arthritis develops in some goats. Serum antibodies do not increase but local antibody can be obtained from synovial fluid of the affected joints. Experimental conjunctival disease can be induced more readily in adult goats than young immature goats. Immunological data obtained do not indicate that definite immunity is acquired.

Proposed Course: Continuation

J. Eye disorders conjunctivitas, keratoconjunctivitis; arthritis; Reiter's syndrome; immunity, cellular, lymphocyte transformation; bacteria, mycoplasmatales, mycoplasma; models, biological; mammals, ungulates, goats.

K. None

L. Manuscript in preparation

1. Primate Quarantine Unit
2. Animal Center Section
3. Poolesville

PHS-NIH

Individual Project Report  
July 1, 1974 through June 30, 1975

- C. EVALUATION OF EFFICACY OF M. bovis PPD TUBERCULIN TO DETECT TUBERCULOSIS IN WILD CAUGHT INDIAN Macaca mulatta
- D. None
- E. David M. Renquist
- F. Donald W. Johnson  
L.D. Konyha  
Albert E. New
- G. Animal and Plant Health Inspection Services  
USDA, Hyattsville, Maryland (Ames, Iowa)  
Department of Veterinary Clinical Sciences  
University of Minnesota, St. Paul, Minnesota
- H. Total: 0.12  
Professional: 0.07  
Others: 0.05
- I. Objectives: To determine the efficacy of Mycobacterium bovis purified protein derivative (PPD) tuberculin as compared to that of the standard veterinary mammalian tuberculin in the early detection of naturally acquired tuberculosis in rhesus monkeys.

Methods Employed: Approximately 50 tuberculous monkeys, identified during routine testing, will be placed in isolette cages and their comparative reactivity to veterinary tuberculin and PPD will be determined. Twelve to 20 fully conditioned, tuberculosis-free monkeys will then be paired with tuberculous monkeys. Each pair will be tested at weekly intervals with specific dilutions of veterinary tuberculin and PPD. Skin reactions will be measured and photographed and lymphocyte transformation studies performed. When tuberculosis is diagnosed in the conditioned monkey, the pair will be killed and necropsies will be conducted. The results will be recorded and tissue samples will be collected for histopathologic evaluation and Mycobacterium isolation and identification.

Major Findings: Data are insufficient to provide details.

Significance: No determination because of insufficient data.

Proposed Course: Continuation

- J. Immunological tests and immunoassay, tuberculin tests; actinomycetales, mycobacterium tuberculosis; mammals, primates.
- K. None
- L. None

Serial No. Z01 RS 00015-01 VR  
1. Veterinary Resources Branch  
2. Office of the Chief  
3. Bethesda

PHS-NIH  
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C. DEFINING THE NUDE MOUSE MODEL

D. None

E. Robert A. Whitney, Jr.

F. Carl T. Hansen  
James R. Ganaway  
Anton M. Allen  
C.K. Hsu  
Robert Purcell  
Paul Holland

G. Department of Laboratory Animal Medicine  
Johns Hopkins University, Baltimore

Laboratory of Infectious Diseases, NIAID

Blood Bank, Clinical Center, NIH

H. Total: 0.3  
Professional: 0.2  
Other: 0.1

I. Objective: To determine the susceptibility of the nude, athymic mouse to viral, parasitic, and bacterial diseases, and to define the role of the thymus activated "T" lymphocytes in susceptibility and pathogenesis of infectious diseases.

Methods Employed: Weanling nude mice are transferred directly from the Building 14G barrier to presterilized, germfree isolators. Protecting this highly susceptible animal from the conventional environment with the flexible plastic isolator system has proven extremely successful. Many nudes, who have a 4-month life span in conventional animal quarters, are still surviving after 15 months in our isolator system.

This project originated as an attempt to infect nude mice with human hepatitis A and hepatitis B. Serum from a human known to be infected with "B," and from a chimpanzee known to be infected with "A" was injected I.V. into separate groups of animals.

Major Findings: In collaboration with Johns Hopkins University, nude mice in isolators were also exposed to known numbers of infectious Schistosoma larvae. After over 12 months' of testing for the antigen and antibody for B and for liver enzyme changes associated with A infections it was concluded that, despite their lack of a cellular immune response, the nude, athymic mouse is not susceptible to human viral hepatitis. In the schistosoma work, nudes, while developing heavy infections, do not show the tissue granulomas seen in conventional mice infected with schistosomes. This demonstrates the role of cell mediated immunity in the pathogenicity of this disease.

Significance: This congenital, athymic state, with its resulting lack of cell mediated immunity in the nude mouse, may be one of the most significant events in the evaluation of animal models for human disease. It must be defined in a number of areas to realize its potential and limitations in biomedical research.

Proposed Course: Continuation

- J. Models, biological; man, mice; immunity, cellular immunity.
- K. None
- L. Two manuscripts in preparation.

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